Evaluation of Interventions to Reduce Child Mortality From Acute Respiratory Infections in a Remote Community in North Eastern Afghanistan, and the Implications for the Emergence of Antibiotic Resistance in *Streptococcus pneumoniae*

Thesis

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No material in this thesis has previously been submitted for a degree or any other qualification at this University or another institution, and no parts have been published.

Eleanor Duncan did some of the questioning and data collection in households in the survey conducted in 2002, and helped with the analysis of this data (section 2.1.2). Dr Bruno Pichon at the Health Protection Agency did the multi-locus sequence analysis of samples of *Streptococcus pneumoniae* sent to the UK from Afghanistan (section 2.4.12). Dr Chris Lane did location mapping of antibiotic susceptibilty, and its interpretation (section 2.1.13).

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Abstract

There are many remote regions of the world where there are no data about the health of the community. This thesis reports on the implementation of a community health programme in Wakhan District, a remote valley in Afghanistan. This programme trained illiterate women to educate mothers to feed their children appropriately, to treat dehydration and to manage acute respiratory infections (ARI) with co-trimoxazole. The programme covered 6000 people in 28 communities, and took five years to establish. Data about births and deaths were collected in 2002, before the programme began, and during its implementation from 2005-8.

ARI was a leading cause of death in children under five. Standard case management of ARI in children, using co-trimoxazole, was effective in significantly reducing mortality. A simple algorithm for appropriate use of co-trimoxazole, based on counting respiratory rate, can be implemented by health workers with limited training. Comparing data collected in 2002, before the programme was implemented, with data collected 2005-8, mortality in children under two years fell by 40%, from 262 to 158 per 1000 live births.

There is little data on the consequences of using standard case management of ARI by health workers with limited training on the reduction of antibiotic susceptibility, or the clinical consequences of reduced antibiotic susceptibility. Isolating invasive *Streptococcus pneumoniae,* (the most common pathogen causing ARI in children) to examine its antibiotic susceptibilities is difficult. Two sets of nasopharyngeal samples were collected from healthy children to give an estimate of the proportion of *Streptococcus pneumoniae* with reduced antibiotic susceptibility. *Streptococcus pneumoniae* isolates were tested for antibiotic susceptibility in a purpose-built laboratory in Wakhan.

Streptococcus pneumoniae was isolated from 47% of the children sampled. 17% of samples showed resistance to penicillin, 70% to co-trimoxazole, 9% to erythromycin and 40% to tetracycline. 16 isolates were sent back to the UK. Six of the 11 which survived were of serotypes not included in the commercially available protein conjugate vaccines. Three were novel strains of *Streptococcus pneumoniae* on multi-locus sequence typing, displaying two different strain types.

The conclusion of this research programme is that health workers with very limited training can successfully implement a simple algorithm to treat ARI in children. It is possible to monitor antibiotic susceptibility in a remote area, with limited equipment, facilities and supplies. In vitro reductions in susceptibility to co-trimoxazole are noted, but the clinical significance of this is unclear. Unusual strains of *Streptococcus pneumoniae* are circulating in this community, which are not covered by vaccines currently available.

Table of contents

1. Introduction

1.1 International Health Inequalities

1.1.1 Child mortality in the developing world

In 2008, 8.8 million children died before their fifth birthday (UNICEF 2009, 1). The United Nations Children's Fund lists the mortality rates for 198 nations (UNICEF 2009, 2). In Sweden, for every 1000 children born alive, three die before their fifth birthday. In the UK, six die. In Afghanistan, the national rate is the second worst in the world - 257 per 1000 die before reaching five years old. The average for the 67 least developed nations is 167 per 1000, whereas the average for the Industrialised World is 10 (UNICEF 2009, 3). Life Expectancy at birth in the UK is 79 years; in Afghanistan, it is 44, largely because of high child mortality.

The leading causes of death in children under five globally are diarrhoea and acute respiratory infection (ARI).

1.1.2 The Millenium Development Goals

In September 2000, 189 heads of state adopted the UN Millennium Declaration and endorsed a framework for development. The plan was for countries and development partners to work together to increase access to the resources needed to reduce poverty and hunger, and tackle ill-health, gender inequality, lack of education, lack of access to clean water and environmental degradation.

They established eight Millennium Development Goals (MDGs). These were a series of targets for improvements in 8 development parameters. Targets were set to be met by 2015, and a number of indicators for monitoring progress were identified. All goals and their targets are measured in terms of progress since 1990.

Development Goal 4 aims to reduce child and maternal mortality, framed in the UN Assembly Resolution 52/2/III.19 "By the same date (2015), to have reduced maternal mortality by three quarters, and under-five child mortality by two thirds, of their current rates."

In September 2009, the United Nations published the Millenium Goals Report. In the Foreword, UN Secretary General, Ban Ki Moon stated "We have made important progress in this effort, and have many successes on which to build. But we have been moving too slowly to meet our goals" (United Nations 2009, p3). The Report outlines progress made, and re-iterates the commitment made by the Industrialised Nations of the world, especially the Group of 8, to invest in development to meet the MDGs, but also warns that the downturn in the global economy may have serious effects in delivering the aid investment required.

As UNICEF Executive Director Ann M. Veneman says, "While progress is being made, it is unacceptable that each year 8.8 million children die before their fifth birthday" (UNICEF 2009 (1)).

This thesis reports on a project in North East Afghanistan, which set out to reduce child mortality, in line with Millenium Development Goal 4. The project has worked to reduce the mortality from pneumonia by implementing a World Health Organization illness case management protocol, in one of the poorest communities in the world, and to examine the effect of the implementation of those protocols on the susceptibility to common antibiotics of one of the disease-causing organisms.

1.2 Introduction to Wakhan District

The research in this thesis took place in the communities adjacent to the Amu Darya (Oxus River) in an area 120km long in the middle third of Wakhan District of Badakhshan Province. This section provides an introduction to the social and cultural geography of the area. Map 1.1 shows the location of the area.

Map 1.1 Wakhan, Afghanistan and surrounding region

1.2.1 Introduction to the area of research

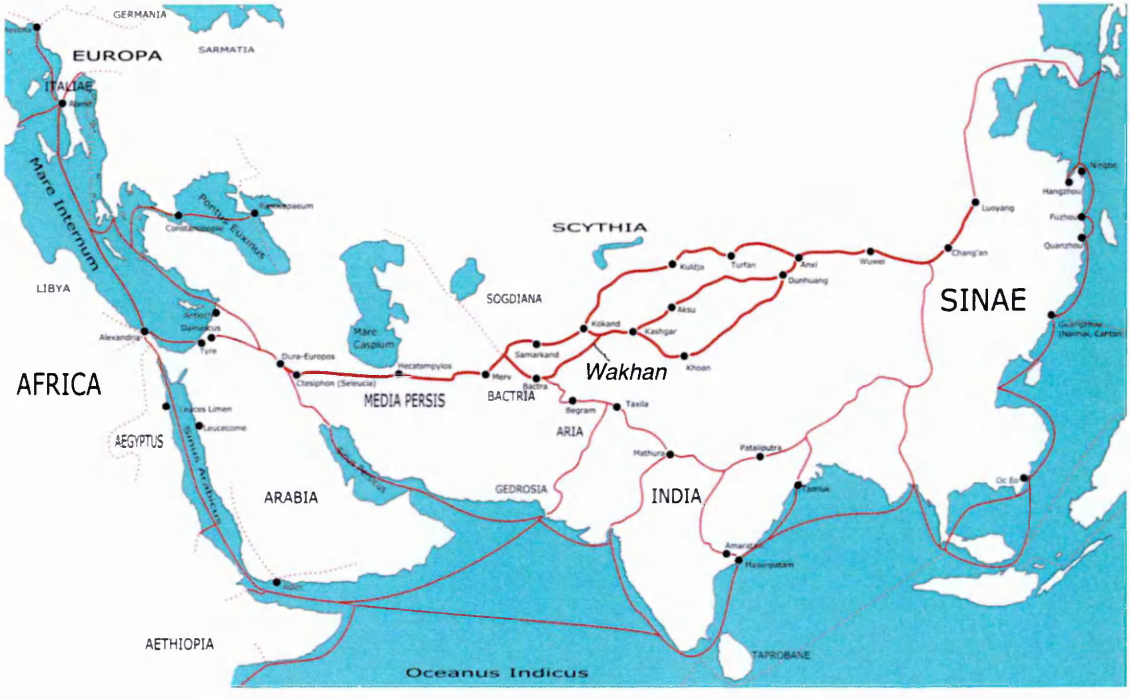
Wakhan District of Badakhshan Province is the most eastern district of Afghanistan. It is a narrow finger of land extending north-east from Badakhshan for 300km. The southern border with Pakistan runs along the crest of the Hindu Kush mountain range. The northern border with Tajikistan runs along the Amu Darya to its confluence at Gaz

Khan 120km from Ishkashem at the western end of the district, and thence along the northern branch to Zor Kol, the lake regarded as the source of that branch. In the very far east, there is a 25km border with Xianking Province of the People's Republic of China. The most of the population of the district are of an ethnic group called the Wakhi, who number around 12 000. They live in villages along the river, at an altitude rising from 2600m at Ishkashem in the west to 3400m at Sarhad-e-Boroghil at the end of the road running along the southern branch of the river, 200km east of Ishkashem. Between the northern and southern branches of the river, lie the Great Pamir Mountains, and to the east of Sarhad-e-Boroghil lie the Small Pamir Mountains. Approximately 1400 semi nomadic people, who are ethnically Kirghiz live in the Pamir areas. These areas are locally known as the 'Bom-e-Dunya' - the Roof of the World.

1.2.2 Historical context

The existence of a thin strip of Afghanistan sandwiched between Tajikistan and Pakistan is a result of 19th century geo-politics. The consequence of the events outlined here is that the population of Wakhan has become an isolated and under-privileged community. This section is mainly drawn from three sources, 'The Great Game; The Struggle for Empire in Central Asia' by Peter Hopkirk (Oxford University Press, 1991), 'Where Men and Mountains Meet: the Explorers of the Western Himalayas, 1820-75' by John Keay, (John Murray 1977) and 'Shooting Leave; Spying Out Central Asia in the Great Game' by John Ure (Constable and Robinson, 2009).

Between 100 BC and 1500 AD, traders on "the Silk Road", bringing goods overland from China to West Asia and Europe, via Central Asia, took many different routes for security and supply reasons. Wakhan was heavily used by traders on the Silk Road at various times. Map 1.2 shows the main medieval silk routes.



Map 1.2 The Medieval Silk Routes
(http://en.wikipedia.org/wiki/File:Transasia_trade_routes_1stC_CE_gr2.pn)

In 1271, Marco Polo, the Venetian traveller, wrote of travelling through the kingdom of Wakhan on his way to China.

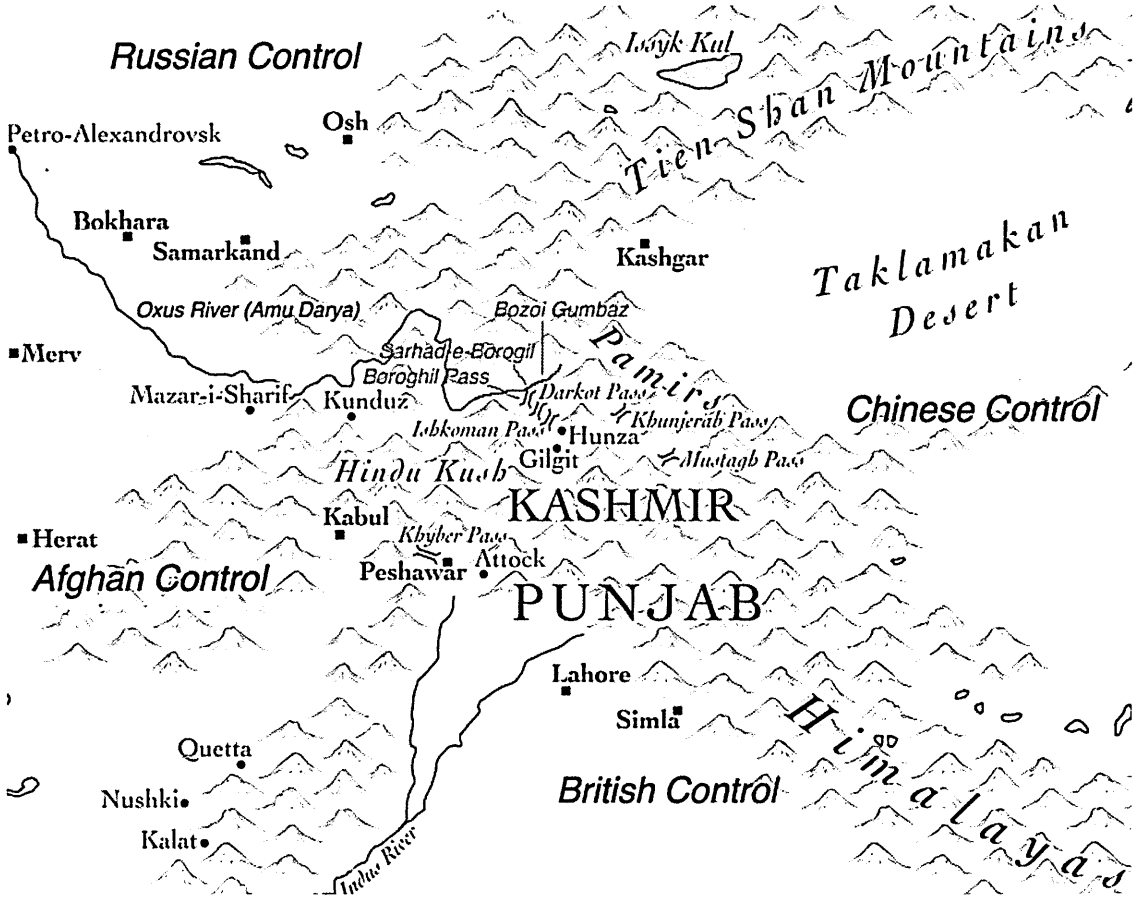
".... you come to a province of no great size, extending indeed no more than three days' journey in any direction, and this is called VOKHAN. The people worship Mahommet, and they have a peculiar language. They are gallant soldiers, and they have a chief whom they call NONE, which is as much as to say Count, and they are liegemen to the Prince of Badashan (sic).

There are numbers of wild beasts of all sorts in this region. And when you leave this little country, and ride three days north-east, always among mountains, you get to such a height that 'tis said to be the highest place in the world! And when you have got to this height you find [a great lake between two mountains, and out of it] a fine river running through a plain, clothed with the finest pasture in the world; insomuch that a lean beast there will fatten to your heart's content in ten days. There are great numbers

of all kinds of wild beasts; among others, wild sheep of great size, whose horns are a good six palms in length." (Polo, M.)

Long distance trade along the route almost disappeared in the years after the disintegration of the Mongol Empire in the late 15th century. The rise of the Ottoman Empire in west Asia, and the increase in European sea trade contributed to this as did the advent of the Black Death.

In the early 19th century, concern grew in the British Government about the influence and intentions of Imperial Russia in Central Asia, and the threat posed to British India. Various exploratory expeditions were sent out, both of British officers with a diplomatic and exploratory agenda, and also highly trained Indian surveyors sent covertly to make maps and spy out these territories beyond the northern frontiers of India. Map 1.3 shows areas of control and strategic places and mountain passes during this struggle.



Map 1.3 The Great Game Region, 1800-95 (adapted from 'Shooting Leave' by John Ure and reproduced with kind permission of Constable and Robinson Ltd)

In the winter of 1837-8 Lt John Wood set out to explore the Amu Darya, or Oxus River. His mission was to find out how far the river was navigable for troop transport and supply, and also to find its source. On 19th February 1838, having travelled up Wakhan, he stood on the ice-covered Zor Kul, the source of the northern branch of the Amu Darya. He knew that Marco Polo had passed that way, and was impressed by the bleakness of the landscape.

In 1868 Mirza Pundit, a specially trained Indian surveyor, went to Wakhan during a journey to survey the passes across the Hindu Kush mountains. At that time, much attention was focussed on Kashgar, (now in the most westerly province of China, Xianking) where the ruler Yakub Beg, was maintaining his independence from Peking, and trying to play London and St Petersburg off against each other. In addition to this, Britain feared that the Russians wanted to annex the independent Khanates of Turkestan, in what are now the former Soviet Central Asian republics of Turkmenistan, Uzbekistan, Tajikistan, Khirgizstan and Kazakhstan. In an attempt to clarify the situation, and protect the northern approaches to India, the British managed to get the Russians to accept that Badakhshan and Wakhan were naturally part of Afghanistan, rather than part of the Khanate of Bokhara, north of the Amu Darya, now in Uzbekistan. In January 1871, the Russians accepted this, thus agreeing Afghanistan's northern border at the Amu Darya. However, Britain's perceived diplomatic victory here was soon trumped by the Russian annexation of Bokhara in 1873.

The Russian presence in Bokhara raised many questions, not least of which was the ability of a Russian army to enter India over passes in the almost unknown, and unexplored area known as the 'Pamir Knot', now in the eastern end of Wakhan District and adjoining areas of Tajikistan and Pakistan. This area west of the Karakoram range extended to the eastern border of the recently annexed Khanate of Bokhara. It was nominally under the control of Yakub Beg in Kashgar. In 1873, a British diplomatic mission to Yakub Beg failed to make any headway concerning his relationship with Russia, but did manage to persuade him to allow Lieutenant Colonel Thomas Gordon to return to Kashmir through the Pamir. He reported in 1874 that the passes at Boroghil in Wakhan and Ishkaman in the Pamir would be passable by a modern army without too much difficulty, posing a real threat to the northern borders of India. More worryingly, he reported that Yakub Beg's Kashgar territory in the east, and supposed

Afghan territory in the west in Badakhshan, did not actually meet, and that there was a 50 mile gap, through which the Russians could pass without offending either.

In the summer of 1889, Francis Younghusband, a British Army officer who by then had become one of the foremost explorers of the region, met a Russian officer in Hunza just south of the Ishkaman Pass, whose map had the 'Pamir Gap' marked in red, indicating a Russian claim on it. By this time, Yakub Beg was dead and Kashgar was once again under Chinese rule from Peking. The Pamir Gap question became even more pressing. Younghusband was dispatched to Kashgar to try to persuade the Chinese to send troops into the Pamir and claim the area to be under Chinese rule. However, Russian spies in Kashgar got wind of this. Rumours started to circulate in London, that the Russians themselves intended to claim the area by force. In July 1891, Younghusband travelled to the Pamir, where, at Bozoi Gumbaz, he met a group of 30 Russian troops, commanded by a high ranking and distinguished officer, who informed him that St Petersburg was annexing the Pamir, including areas which were unquestionably under either Afghan or Chinese control. Younghusband himself was then 'expelled from Russian territory', although the area where they met had been previously accepted as Afghan territory. This action provoked outrage in London and the diplomatic storm rattled the Tsar and Government in St Petersburg; facing famine and increasing political unrest in many areas at home, they did not have the stomach for a big row about remote mountain valleys in the furthest south eastern corners of the Empire, and the Russian claim to the area was withdrawn. However in 1892, the Russians mounted a raid on an Afghan Border post in Somantash in the far east of supposed Afghan territory in the Pamirs, as if to restate their claim.

Col Algenon Durand, the British Representative in Kabul in 1893-4 persuaded the King of Afghanistan, Abdur Rehman, to retain control of Wakhan. Abdur Rehman had taken

control of Badakhshan a few years earlier, when he conquered the northern areas of Afghanistan controlled from Kunduz. Following the Somantash raid, he was reluctant to hold on to Wakhan, feeling that his authority was stretched, but Durand prevailed. Anglo-Russian negotiators demarcated the border along the Amu Darya and persuaded Kabul to withdraw from any territory on the north or eastern side of the river, and the Emir of Bokhara, now a vassal of the Russians, to withdraw from areas south of the river. An Anglo-Russian border commission met in Great Pamir in summer of 1895, and fixed the current international borders; representatives of the Afghan Government were in attendance but took no part in the negotiations.

Wakhan once again faded into obscurity. Some trade caravans were able to pass through Wakhan until the 1930s, when the northern border with the USSR (now independent Tajikistan) was sealed, and in 1948, the Chinese Sianking border was also sealed following the Communist takeover in China.

In the 1960s, a road was built 100 km into the district, to enable the Afghan Royal Family and other wealthy hunters to travel to Wakhan to hunt Marco Polo sheep, ibex and snow leopards. This road was extended another 100km and four substantial bridges were built over the southern branch of the Amu Darya in the early 1970s. After the Russian invasion of Afghanistan in 1979, a substantial military post at Sarhad-e-Boroghil was established to guard the Pass into Pakistan.

Although always a remote area, Wakhan benefited for centuries from occasional trade caravans passing through. After the borders closed, even this sporadic trade ceased. The Wakhi were left to themselves, isolated and largely ignored.

In the last 100 years, there has been very little movement of people, and very little contact with the outside world. This isolation has led to very poor provision of services, and very little trade. The scarcity of trade means that commodities are very expensive, and some commodities, such as fertiliser, are unavailable. In turn, this situation increases the poverty of the community, and health risks to children in particular.

1.2.3. The physical and social environment of Wakhan

This section draws on the observations made by the author during the time he lived in Wakhan from 2002-8, which was the period during which data for the study was collected, although these observations do not include data collected for the study. This section also draws on the detailed anthropological studies by Shahrani and Kreutzmann.

Mohammed Nazif Shahrani, was born in Badakhshan Province in Afghanistan, and completed his education in the USA. He is now Professor of Anthropology in the University of Indiana. For his PhD research, conducted in 1975-76, and published in book form in 1979, Shahrani studied the interaction between the Kirghiz living in the Pamir and the Wakhi in the valley bottom.

Hermann Kreutzmann holds the Chair of Cultural Geography and Development Studies and is director of the Institute of Geography at the Friedrich Alexander University in Erlangen-Nuernberg, Germany. Since 1996, he studied the Wakhi in Pakistan and Afghanistan.

Topography

Wakhan District is a high mountain valley system, covering 8936 sq km, at a minimum altitude of 2200m, rising to the highest peak at 7485m. The valley bottom, which is cultivated, rises to 3400m.

Shahrani divides the land in the valley bottom ecological zone into 7 types:

jangal - dense scrubland,

dargaw/sail - alluvial deposits, usually in fans, often with large boulders, from side rivers from glaciers and snow melt in the mountains on the sides of the valley. A *dargaw* is literally a side stream, and a *sail* an area which has been flooded by a *dargaw,* or which has has a mud slide caused by a *dargaw.*

raig - sand deposits,

maghzar - grassland directly watered by a *dargaw*, often poorly drained.

kesht gah - agricultural land, divided into small fields irrigated by channels diverting water usually from a *darghaw,* but occasionally from the main river

dasht - dry uncultivated land, made up of rocks and dust

koh - mountainside

Kesht gah and *marghzar* make up around 15% of the land area in the valley bottom ecological zone. (Shahrani, 1976 p8). This is the only land which is economically productive, *kesht gah* for cultivation of crops and *maghzar* for grazing.

In the upland Pamir areas, the land is mainly *dasht* and *koh,* with some areas of *maghzar* in the summers, fed by snow and glacial melt.

Climate

The climate is arid with great differences in seasonal and diurnal temperatures. Precipitation is low, and rarely in the form of rain. The coldest temperature recorded in

Wakhan was minus 25° Centigrade one night in January 2007. The highest summertime temperature recorded in the valley bottom at Kipkut was around 35° Centigrade. This was a very hot day, so the temperature was measured. Shahrani's estimate of 40° is too high. The first frost, freezing standing water, was usually in the first week of September, and the last in late April. Shahrani states that there is little rain . The only significant rainfall between 2003 and 2008, was at the end of May and in early June; this rainfall was not formally measured, but it was sufficient to soak and to leak through the mud roof of the house. Local people said that rain at this time of year of this degree was common.

Population and demography including housing and household size

Kreutzmann states that in the 1920s, a census put the population of Wakhan at 3500, presumably including both Wakhi and Kirghiz groups (Kreutzmann 2004). By the 1970s this had doubled. Shahrani reckoned on 700 households in 1976, and Kreutzmann 1100 in 2003. Neither Shahrani or Kreutzmann give a breakdown by age or sex. Kreutzman quotes a local official estimating the total population to be around 13500 in 2003. Kreutzmann states average household size to be 8-11 (Kreutzmann 2004). The figures the author was given are in line with this, the whole district consisting of 1200 households. In the survey conducted in 2002 by the author, the mean household size was 11.1 people.

Language

As described by Kreutzmann (2004) and Shahrani (1979), the Wakhi speak a language called *khikwar* or *sposik* by themselves, and *Wakhi* by others. Wakhi belongs to the Pamiri language group of the Eastern Iranian branch of the Iranian languages within the Indo-Iranian group. It is not mutually comprehensible with other local or national languages. There are about 40 000 Wakhi speakers in the region, 12 000 in Afghanistan and the rest in Pakistan, Tajikistan and Xianking Province of China. The

Wakhi community in Pakistan have developed a modified Latin script for Wakhi, and there is a small corpus of literature published in Wakhi. This is inaccessible to the Wakhi in Afghanistan, and Wakhi is not written in Persian/Arabic script at all.

Most adult men speak Dari (the Afghan dialect of Farsi, or Persian, and one of the two national languages of Afghanistan) to some degree, although some older men speak very little Dari. Few women speak more than very rudimentary Dari. All education is supposed to be in Dari although in the first and second years, the teacher translates into Wakhi much of what the children are reciting.

The author of this thesis learned to speak Dari to a good level, was able to read and write at a basic level, and also learned very rudimentary Wakhi.

Education

Kreutzmann observed the schools in Wakhan, noting that 'the quality and effect of education is appalling'. He noted that none of the teachers had any training, and many were barely literate themselves. They also had not been paid for 8 months. Most classes happened in tents supplied by UNICEF, as the buildings used previously were in such bad repair as to be unusable. In classes 1-3, 40% of the pupils were girls, classes 4-7 around 30%, and thereafter, almost no girls went to school.

A survey conducted by the author in 2002 showed that 14% of men and 2% of women had received more than 1 year's schooling. No-one in the area surveyed had received any education beyond the end of high school.

In the households surveyed, 60% of the 7-14 year-old boys and 22% of the 7-14 year-old girls were in school. None of the girls in school is over 15 years of age, whereas

boy students can be as old as twenty. Most girls are married by 16 years old, and once married, have responsibilities in the household.

Diet and household life

All houses in Wakhan have basically the same design; an approximately square house consisting of a lower area, surrounded by platforms covered in rugs, and on one side, a clay 'tandoor' hearth and a kitchen. Very little wood is used for fuel, brushwood from a thistle-like plant, a mountain shrub, akin to heather or lavender and dung being mainly used. Smoke escapes through a square hole in the roof above the tandoor.

The layout of the home, with the central tandoor below the small smoke exit hole, means that when the tandoor is lit (mid-morning and evening), the houses fill with smoke very rapidly. Many older people, especially women who sat over the fire cooking, reported respiratory problems. An attempt was made to make a quantitative measurement of the particulates in the home atmosphere over a 24-hour period; unfortunately, the electrical power required to run the monitor was too unreliable, and the monitoring was abandoned.

Wakhi families eat four meals a day; an early breakfast, a mid-morning meal, lunch and an evening meal after it gets dark. Every meal consists of bread and salt tea with milk. If they can afford it, some families will eat plain rice with oil in the evenings. Most bread is made from wheat flour. In the months before the wheat harvest, wheat may be in short supply, and bread made with barley flour is eaten. After the peas are harvested in July, bread made with a mixture of pea and barley flour is eaten.

Agriculture

The soil is very sandy and contains little organic matter. A soil analysis done in 2007 by an agricultural consultant visiting Wakhan (the sample being sent to the UN Food and Agriculture Organization in Islamabad in Pakistan) showed a number of minerals, particularly potassium, to be lacking. Most years, no commercial fertiliser is available, and the only enrichment of the soil is from spreading animal dung.

In the lower part of the valley, wheat, barley, peas and beans are grown, with some millet. In the upper part of the valley where the author lived, only three villages at the lower end of the area grew any beans at all, and millet was only grown in two villages at the lower end, on the north (i.e. south-facing) side of the river. The land is irrigated twice a week until two weeks before the harvest. Irrigation is by flooding the fields, in which the soil has been ploughed into ridges 15cm high and 20cm apart. The irrigation water comes either from glacial melt streams running down the sides of the valley, or the main river and runs through the channels between the ridges. This method results in a lot of organic matter being washed out of the soil, further degrading it.

The lower and south-facing villages start ploughing and sowing peas in late April or early May, sowing barley in early May and wheat in mid to late May. The peas are harvested in July, the barley in late August. The higher, more eastern villages follow on up to three weeks later. In the lower areas the wheat harvest starts in early September, and starts three or sometimes four weeks later at the top of the valley. At the top of the valley at 3400m, the wheat does not ripen at all in three or four years out of ten. The crop is cut by hand, then threshed by donkeys or bullocks, and winnowed by hand. From the beginning of the barley harvest to the end of the wheat harvest takes about six weeks. Early snow (the earliest experienced by the author was 9th October) can cause significant problems for threshing and winnowing.

In 2002-8, local farmers told the author that a poor crop might be three times the seed sown, and a good crop, seven or eight times. With fertiliser, when it was available, this amount might double to 15 times. The median landholding is 2-3 *jeribs* (0.44-0.66 of a hectare). This requires 70-105 kg of seed, and yields between 200 and 800 kg of grain without fertiliser, and up to 1500kg of grain with fertiliser. An average household of 11 people requires 6 kg of flour a day to make bread, or at least 2000kg per year. This shows that the majority of families cannot grow enough to eat, and have to rely on trading animals, or earning cash, to make up the shortfall. One adult sheep could be exchanged for five or six 50kg bags of wheat in 2007.

Both Shahrani and Kreutzmann discuss animal husbandry, both stating that in the upper part of the valley, herding is of greater importance than in the lower part. The population is transhumant, in that in the summer, some of the population moves up onto high mountain pastures to graze the sheep and goats for the summer months. The animals are fed on the lush pastures, and butter, clarified butter and dried yoghurt are made for consumption over the winter. Most families have a cow to provide milk for tea and in the plentiful summer months, any surplus is used for yoghurt or butter. Some wealthier families have yaks, which stay in the high mountains all winter. The cows are milked. Most male calves are castrated and either used for transport or sold for meat. A few males are kept as breeding bulls; these are very aggressive and have to be kept apart from the rest of the herd except when serving the cows.

Other employment and income sources

Shahrani describes patterns of migrant labour; men from poor families may travel to towns in Badakhshan to work in construction, load carrying or other menial casual labour for cash, especially over the winter months. Those without land also work for other wealthier neighbours in agricultural labour (Shahrani, p74). By the time Kreutzmann studied the community, these patterns had changed somewhat; internal

insecurity in Afghanistan had made winter sojourns for cash in Badakhshan towns less common. The wages paid were also very low, so that no savings could be returned to Wakhan, although while the worker was away, there was one less mouth to feed. Some from the upper part of Wakhan would cross the Boroghil Pass into Pakistan, to seek work in the Ismaili community of the adjoining area, but many found there was little opportunity to save and return cash to Wakhan. After September 2001, the Pakistani authorities also made it more difficult for Afghans to travel freely into Pakistan. Kreutzmann also details other economic activities for which the Wakhi 'pay' in kind, such as milling grain or weaving.

The survey of 2002 for this research programme revealed very little migrant labour. One family had a son who was in Chitral in Pakistan, but he had been away for 2 years and had never sent anything back. Several families reported men having worked as migrant labourers in the past, but the returns being small.

The only salaried positions given in the survey were those of school teachers and border security officials. Most of the border security force are local people; boys aged about 17 are conscripted for two years, and some remain in the force after the time is up. However, salaries for both teachers and security personnel are low and usually paid late, if at all. All the school teachers were also involved in agriculture.

Some construction projects provided some income, either as cash or as 'food for work'.

Men from families with little or no land or livestock worked for other wealthier families in agricultural tasks, being paid either in kind or in cash. Both agricultural and labouring work paid about US$ 3 per day. This was enough to buy about 7 kg of wheat flour, which might feed a family of five for one day.

Trade

Kreutzmann describes at length the trading relationships of the Wakhi, and the author's observations were very similar. Essential foodstuffs, such as grain or flour, cooking oil, rice, tea and salt, and other goods, such as clothing, rubber boots, and cooking and eating utensils are exchanged for livestock with travelling traders, who come in trucks from April to November. Most come in the spring, and will exchange goods for livestock, but will not take the livestock until after they have been fattened up over the summer in the Pamir or other high pastures. Kreutzmann details the rates of exchange, showing that the Wakhi often get a rather raw deal.

Wealth and poverty

Kretzmann compares levels of wealth and poverty in 2003 with Shahrani's survey of 1976. Of 700 households in Shahrani's survey, he estimated there to be 30 households (4%) who were affluent, 600 (86%) to be 'medium well off' (sic) and 70 (10%) to be 'pauperized' (impoverished). Kreutzmann estimated that in 2003, there were 1100 households, of which 112 (10%) were affluent, 200 (18%) were medium well-off and 800 (72%) were pauperized. Kreutzmann says 'Poverty in this context cannot be measured in categories of monetary income. A pauperized household is defined as a living community which is in no position to generate sufficient food for a meagre subsistence by their means of production. All those households are dependent on external food supplies and/or grants from welfare institutions for their survival.' Shahrani equated this situation with landlessness (Shahrani p64 footnote).

The consensus of the communities amongst whom the author worked was that the number of households struggling economically had increased over the last 20 years.

1.2.4 Recent Surveys by other organisations

Afghan Aid survey 1998: anecdotal report of high mortality and poor service provision

In 1998, a team of two workers from the British funded charity Afghan Aid travelled to Wakhan. They reported their observations, but there was no quantitative data. They observed high levels of poverty and reported high child mortality and poor nutrition and the total absence of assistance from outside sources. The survey report was not published, but a copy was given to the author of this thesis.

Assessment Mission of Médecins Sans Frontières (MSF) June 1999

An Australian doctor working for MSF in Ishkashem, a town west of Wakhan, travelled into Wakhan in June 1999, with a nurse and a local logistics officer, who also acted as translator. The survey report was not published, but a copy was given to the author of this thesis.

The team measured mid upper arm circumference (MUAC) on 346 children. MUAC is an internationally recognised proxy for nutritional status in children aged 6-59 months; MSF use less than 11 cm for 'severe malnutrition', 11-12.5 cm for 'moderate malnutrition', 12.5-13.5cm for 'mild malnutrition (MSF, 1999. p42). They found 46% of children to be malnourished, of whom 31% were mild, 14% moderate and 1% severe.

MSF reported good coverage for National Polio Campaign immunization in most villages in the valley floor, but poor coverage in villages due to lack of supplies. Coverage of the Kirghiz population in the Pamir areas was unknown. The MSF team

also reported on measles and diphtheria outbreaks in 1996 and 1997, although the author did not explain how the team decided on these diagnoses.

Focus (Aga Khan Foundation) Nutrition Survey 2001

The Ismaili Charity Focus conducted a nutrition survey in ten areas of Badakhshan Province, one of which was Wakhan. The team examined 516 children in Wakhan District. The villages in which this was done were not reported. They found that 2.9% had oedema; 7.7% were wasted with low weight for height, of which 1.5% were severely so; 59.6% were low weight for age, 23.7% of whom were severely so; and 71.2% were low height for age. The definitions of each of these criteria were not published in the summary made available to other charities. The survey report was not published, but the author of this thesis was given a two-page summary of the survey report at the Focus Office in Faizabad, the provincial capital of Badakhshan.

1.2.5 Start of my interest in Wakhan

Orphans Refugees Aid International (ORA) was an international relief agency based in Germany. In 1990, ORA opened a narcotic addiction rehabilitation centre in Peshawar, north-west Pakistan, catering mainly for Afghan refugees. After one year's operation, the centre management noticed a disproportionate number of addicts travelling to Peshawar for rehabilitation from the districts of Badakhshan Province bordering Tajikistan and Pakistan. A survey team was sent to the area, which discovered a very high proportion of the population addicted to opium, up to 60% of adults in some areas. In 1995, rehabilitation work was started in the area, and in 1996, a centre was opened in Khandud in Wakhan District.

In December 1994, I visited Peshawar and spoke with the rehabilitation project leader. In Badakhshan, most addicts started to use opium when they were ill, since no other medical assistance was available, and thus became addicted. The ORA leadership had decided to try to set up a medical programme in the area to prevent the sick using opium. In 1997, I made a brief visit to Badakhshan, and decided to volunteer for the task of setting up the programme. After further training, I moved to Peshawar in 1999, and visited Wakhan in the summer of 2000. In the summer of 2002, I led an ORA team conducting a survey in Wakhan, and from June 2002 until June 2008, I lived with my family in Wakhan.

1.3 Situation of analagous populations

Extensive literature searching has not found a descriptive account of mortality and causes of mortality in a community analagous to the one studied in Wakhan.

UNICEF and WHO publish national statistics for mortality rates under one year and under five years of age. For 2008, the under one year mortality rate for Afghanistan was 165 per 1000 live births, and under five mortality was 257 per 1000 live births. The under five rate was the second worst in the world. The figure for the UK was seven deaths per 1000, and the lowest was Sweden at three deaths per 1000 (UNICEF 2009 (2)).

Bryce at al (2005) in a comprehensive review of child death in the developing world estimated that 73% of deaths in children under five were attributable to six causes - pneumonia (19%), diarrhoea (18%) malaria (8%) neonatal sepsis or pneumonia (10%), preterm delivery (10%) and asphyxia at birth (8%). Khan et al (2009) reported an increased incidence of pneumonia in children under five living at higher altitude compared with those at lower altitude in Pakistan (1980-2285 vs 1675-1980m). The

population described in this study is 100km away from the population of Wakhan, and lives in similar conditions. Khan speculates that "Possible explanations for this high rate could include indoor air pollution by wood fires, harsh winters (which necessitate greater time indoors in overcrowded homes), over-diagnosis because of increased baseline respiratory rates at high altitudes, and a true increased risk of disease associated with altitude." (Khan et al p196). Edmonston and Andes studied government statistics in Peru to ascertain which of four factors (community size, female education, access to medical facilities and altitude) had an effect on levels of child mortality; low levels of female education and living at an altitude above 3500m were independent risk factors for increased child mortality (Edmonston and Andes 1983).

Rudan et al (2008) compare mortality rates from pneumonia in different countries in the developing world, and estimate that Afghanistan has the highest mortality rate from pneumonia of any country in the comparison, at 185.9 deaths per 10000 population under five. They cite 'definite risk factors' for this as low weight for age (defined as weight lower than two standard deviations below the mean, otherwise known as a 'z score of less than -2',) low birth weight, non-exclusive breast feeding, lack of measles immunisation, indoor air pollution and overcrowding. They identify further 'likely risk factors' as parental smoking, zinc deficiency, mother's experience as a caregiver, concomitant diseases (e.g. diarrhoea, heart disease, asthma), and 'possible risk factors' as mother's low educational status, day-care attendance, rainfall (humidity), high altitude (cold air), vitamin A deficiency, low birth order and outdoor air pollution.

Low anthropometric measurements predispose to a higher risk of child death (this will be discussed in greater detail in section 1.4.3 below). According to the Global Hunger Index, 23% of children in South Asia are described as underweight (Grebner et al, 2009).

A comprehensive review of the effect of indoor smoke pollution on acute respiratory illness in children was published by Smith et al in 2000. They reviewed 16 studies, nine case-control studies, four cohort studies and case-control fatality study in the developing world, and two case-control studies in the developed world. All of these studies showed an increased odds ratio for ARI in children for these exposed to indoor smoke from biomass used for cooking, the odds ratios varying between 2.2 and 9.9.[1] In these studies, end points were different, and confounding factors were not always adequately adjusted for. However, Smith et al's conclusion was that continual exposure to indoor biomass smoke raised the incidence of acute respiratory infection significantly.

1.3.1 The need for intervention for as many risk factors as possible

These accumulated data show that many poor communities in the developing world show a similar profile of child and maternal mortality, exacerbated by poor nutrition (the assumed cause of low anthropometric measurements), low immunisation rates for measles, overcrowding and indoor smoke pollution. In addition, high altitude may be an independent risk factor. Acute respiratory infection is shown to be a very significant cause of death.

Jones et al (2003) in a review article on child survival estimated that "two-thirds of child deaths could be prevented by interventions that are available today and are feasible for

[1] An odds ratio is an expression of the odds of an event occurring, when comparing two groups. an odds ratio of 2 means that the odds of the event occurring is twice as high in the study group when compared with the control group. In this case, an odds ratio of 2.2 means that child mortality in the group of children exposed to indoor smoke pollution was about 2.2 times that of the children in the group not exposed. The odds ratio approximates the relative risk for rare diseases.

implementation in low-income countries at high levels of population coverage" (Jones et al, p65).

If child and maternal mortality are to be reduced, then as many risk factors for excess mortality as possible should be reduced. Programmes tailored for each community's needs should be designed to improve nutrition, improve immunisation coverage, especially for measles, and reduce indoor smoke pollution. In addition, programmes for treatment of acute respiratory infection, accessible to the population, should be introduced.

1.4 Rationale for intervention design

1.4.1 Introduction to community health ideals

In September 1978, the World Health Organization held the International Conference on Primary Health Care in Alma-Ata, capital of the Kazakh Soviet Socialist Republic (now Almaty, ex-capital of independent Kazakhstan). This ground-breaking conference issued the 'Declaration of Alma-Ata', which had the strap-line 'Health for All by 2000.' (WHO, 1978) The Declaration opened with two startling statements:

I

The Conference strongly reaffirms that health, which is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity, is a fundamental human right and that the attainment of the highest possible level of health is a most important world-wide social goal whose realization requires the action of many other social and economic sectors in addition to the health sector.

II

The existing gross inequality in the health status of the people particularly between

developed and developing countries as well as within countries is politically, socially and economically unacceptable and is, therefore, of common concern to all countries.

These ideals, (described in 2008 by WHO Director General Margaret Chan as 'Utopian' (Chan 2008, p865)) set the tone for an exposition of the necessity of universally accessible comprehensive primary health care, not only providing traditional health service delivery, but also tackling community issues which lead to ill health, such as poverty, clean water and agricultural development.

However, the rush of enthusiasm at Alma Ata was not followed by concerted action. In the cold light of day, it was regarded as unrealistic (Chan 2008). The ideals were perceived as threatening to the medical establishment (Werner and Sanders 1997 p23) and this attitude, combined with a world recession in the early 1980s, meant that attempts at implementation were half-hearted. Health for All did not seem a viable goal. In 1983, UNICEF launched a modified and much more selective programme, called Child Survival Revolution, whose pillars were growth monitoring, oral rehydration, promotion of breast-feeding and immunisation (usually reduced to the acronym GOBI). The following year, three other aims were added, making GOBI-FFF; family planning, food supplementation and female education (Werner and Sanders 1997 p24). The economic recession in the early 1980s squeezed government budgets, a situation made worse by the World Bank's structural adjustment programmes, and a series of WHO 'vertical' programmes, aimed at single diseases, undermined the comprehensive primary health care philosophy and strategy, and took away what little funding there had been. The concept of comprehensive primary health care to be universally implemented by government ended up in the long grass within 10 years of the Alma Ata Conference.

1.4.2 Efficacy of community health worker training programmes to improve mortality

Small scale projects, some run by governments, and others by non-governmental organizations (or 'NGOs', which are usually charitable institutions), did continue after interest in comprehensive primary care waned, and many new ones were established. Interest in their effectiveness grew. 'Health for All by 2000' seemed to be an embarrassing remnant of a past age, but as the Millenium Development Goals were adopted, strategies for achieving them were re-examined. In December 2005 the journal *The Lancet* sponsored the Countdown to 2015 Child Survival Conference in London. Following that, *The Lancet* published a review of the evidence of the effectiveness of community health workers (Haines et al, 2007). The evidence base is very diverse in nature and thus rather difficult to compare and collate, but the conclusions of the review were that training community health workers with limited education for periods of time well short of the time to train nurses or physicians, can be beneficial for child health outcomes, and be cost-effective.

Haines investigates these issues because;

- There is an international shortage of trained medical personnel. Poorer communities are particularly under-served, the extreme example of the 'inverse care law', whereby those with the greatest need receive the least care.

- Several South Asian and African countries are currently investing in a new cadre of community health workers. A statement from a WHO Study Group suggests that "Community health workers should be members of the communities where they work, should be selected by the communities, should be answerable to the communities for their activities, should be supported by the health system but not necessarily a part of its organization, and have shorter training than professional workers" (WHO 1989).

- 60% of deaths in children under 5 (more than 10 million deaths per year) could be prevented by currently available interventions.

- Facility-based services tend to emphasise curative care over prevention. A combination of community-based care, with outreach from facilities, achieving 90% coverage could result in between 18% and 37% reduction in neonatal mortality.

Haines cites the following evidence:

- Various trials have shown the efficacy of 'case management'[2] of ill children by community health workers.

- A meta-analysis of community-based trials examining the efficacy of case management of pneumonia on mortality in neonates, infants, and preschool children suggested an overall reduction of 24%. (Sazawal et al, 2003)

- A trial in Tigray, Ethiopia, of training local coordinators to teach mothers to give antimalarials promptly to their sick children in the home showed a 40% reduction in under-5 mortality (Kidane and Morrow, 2000).

- In India a 7-year trial showed a reduction of more than 50% in neonatal mortality by promoting simple algorithms to be used by community heath workers to detect sepsis and pneumonia in neonates; simultaneous presence of 2 out of 7 clinical signs were 100% sensitive and 92% specific, which led to accurate diagnosis and prompt appropriate treatment (Bang et al, 1999).

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[2] 'Case management' in this context is the use of a simple evidence-based algorithm for the assessment and appropriate treatment of each child presenting to the health worker.

- The performance of community workers compared very favourably with more highly trained health professionals in appropriate management of diarrhoea, and prescription of antibiotics, probably because they follow protocols better. Community health workers achieve higher vaccination rates than clinic outreach teams in both urban and rural areas.

- Several studies show that using supervised community health workers is cost effective.

In addition to this comprehensive review, other evidence for the effectiveness of 'lay' health workers in health promotion has been published by the Cochrane Collaboration (Lewin et al, 2005). This included 43 studies of lay health workers involved in health promotion. 35 of these studies were in the developed world, although of these 15 were interventions aimed at marginalised groups. The comparison was between health promotion by lay health workers (LHWs) and 'usual care'. Promising benefits were shown for LHW interventions to promote immunisation uptake in children and adults (RR=1.30) and LHW interventions to improve outcomes for selected infectious diseases (RR=0.74). LHWs also appear promising for breastfeeding promotion.

The published evidence suggests that training lay members of a community to detect and manage illness in children is effective in reducing mortality, and also cost-effective. This approach was adopted by the project in Wakhan, and was shown to be effective in reducing child mortality from ARI.

The World Health Organization has shown a renewed interest in the possibilities of comprehensive community-based health care. In an editorial in *The Lancet* in 2008, Director General of WHO, Margaret Chan said "Today, primary health care is no longer

so deeply misunderstood. In fact, several trends and events have clarified its relevance in ways that could not have been imagined 30 years ago. Primary health care increasingly looks like a smart way to get health development back on track" (Chan 2008, p866). The 2008 World Health Report, entitled "Primary Health Care; now more than ever", was published in October 2008 and adopted by the World Health Congress in May 2009. (WHO, 2008) It reiterated many of the principles of the Alma Ata Declaration: universal coverage, people-centred services and intersectoral co-operation, and also emphasized the need for coherent public health policy and good leadership. There is almost no specific mention of the role of lay or community health workers. The principles it sets out demonstrate a desire for health equality and universal coverage that can probably only be met using community health workers.

1.4.3 Efficacy of community nutritional interventions and growth monitoring

Anthropometry and 'malnutrition'

Comparison of weight, age and height of a child against a standard value is used to assess nutritional status. Deviation from the mean, is used to 'band' children. This may be expressed as a z score, where a z score of more than 2 standard deviations below the mean is regarded as underweight, and more than 3 standard deviations below the mean, severely underweight. These are often written as a z score of less than -2 and less than -3. Alternatively, bands of percentage deviation from the mean are used.

Effect of anthropometric scores on mortality rates

Mortality rates among underweight children are higher than for children who are not underweight. A meta-analysis of 5 prospective studies showed that children from 6-60 months of age with a weight of 60-80% of the median weight for age of the reference population had a relative risk of 2.2 of dying, and those with a weight of less than 60%

of the reference median weight for age had a relative risk of 6.8 of dying during the follow-up period (between 6 and 24 months). The same meta-analysis estimated that 41% of deaths in children in this age group in the developing world were associated with being underweight (Schroeder and Brown 1994).

Improving nutritional status reduces mortality

There is very little published evidence to show that reducing levels of 'malnutrition', as measured by improved anthropometric scores reduces mortality. Victora et al (1999) used a computer model to predict the effect of improved nutrition on mortality, predicting that reducing the proportion of children with a z score of less than - 2 by 40% would lead to a 5-13% reduction in deaths from pneumonia. Caulfield et al (1999) evaluated 21 programmes to improve infant feeding from 6-12 months of age, and estimated that reduction in prevalence of malnutrition of 1%-19% could lead to a reduction in mortality associated with malnutrition by 2%-13%.

The efficacy of regular growth monitoring

Regular growth monitoring of children up to 3 years of age has been promoted by UNICEF in the years following the Alma Ata Conference. For this reason, it was incorporated into the Wakhan community health programme.

In 2007, UNICEF held a Technical Consultation on Growth Monitoring. In the Introduction the paper states "Starting in the 1980s, Growth Monitoring (GM) was promoted as one of the key components of critical preventive care for young children (GOBI-FFF), and for the two decades since, Growth Monitoring and Promotion (GMP) has been implemented in a variety of contexts as an element of nutrition and health programs" (UNICEF 2007, p3).

The consultation continues "growth monitoring and promotion can have multiple functions:

- As a screening process, it informs caregivers of the child's growth rate and motivates them to take action to promote child growth.
- As an educational and promotional activity, it provides the opportunity to counsel about childcare, feeding, and other topics as needed. The major promotional component of GMP, however, is individual counselling; additional promotional activities are usually designed to link with and benefit from it.
- As a platform for building comprehensive community nutrition and health programmes, GMP serves as an entry point to motivating communities to take action to improve child growth when the community is informed of the results of GM and involved in the process of GMP.
- As a contact point, it allows for delivering other essential health and nutrition services and/or promoting the coverage and utilization of services.
- These services vary by program and setting, and the outcomes from these actions need to be considered separately in evaluation of GMP outcomes" (UNICEF 2007, p6).

However, the efficacy of regular growth monitoring in reducing mortality is unclear. In a Cochrane Review of the published literature on the efficacy of growth monitoring, Garner and Panpanich (1999) could find only two papers of sufficient quality to include in the review. In one, the nutritional status at 30 months in 500 children showed no difference between those allocated to growth monitoring and those not. The other study examined whether counselling improved mothers' knowledge of the growth chart, and reported better test scores at four months. Garner and Panpanich state that "given the level of investment in growth monitoring worldwide, it is surprising there is so little research evaluating its potential benefits and harms."

They continue "Part of the debate about the effectiveness of growth monitoring endures because of lack of clarity over what it is and what its purpose is" (Garner and Panpanich, p199).

The goals of a good programme are to identify children who are failing to thrive, and to use the opportunity of weighing to educate their mothers about appropriate feeding, or to give supplementary feeding. For example, Gerein and Ross (1991) evaluated three growth monitoring programmes in Zaire (now Democratic Republic of Congo), and discovered that the quality of delivery of the programmes was very poor, in that after the children were weighed, adequate education was not given to mothers of those failing to thrive.

Ashworth et al (2008) in a comprehensive review of growth monitoring strategy suggest that there is evidence from small-scale studies in Nigeria, Jamaica, India, and from large programmes in Tanzania, India, Madagascar and Senegal that children whose growth is monitored and whose mothers receive nutrition and health education, and have access to basic child health services have a better nutritional status and/or survival than children who do not. There is some evidence from a large-scale programme in Brazil (de Souza et al, 1999) that participation in growth monitoring confers a significant benefit on nutritional status independent of immunisation and socio-economic status. There is evidence from India (Kapil and Pradhan, 1999) and Bangladesh (Karim et al, 1994) that growth monitoring has little or no effect on nutritional status in large-scale programmes with weak nutrition counselling.

In conclusion, the overall evidence concerning the efficacy of growth monitoring programmes is equivocal; weighing the child and plotting the weight on the chart in

itself is of no value. However, growth monitoring as part of a package of healthcare may in itself confer some benefit, as will be described later in this thesis.

1.4.4 Efficacy of community-based treatments for acute respiratory infections

WHO published recommendations on the management of ARI in children at 'first level' facilities[3] in 1991 (WHO 1991). These were based on an exhaustive review of the published literature on the impact of 'standard case management' on the diagnosis and treatment of acute respiratory infection in children, and seven commissioned research programmes in India, Pakistan, Indonesia, Tanzania, the Philippines and two in Nepal. In the technical paper, the authors quote results from these nine studies, showing a mean reduction in death from acute respiratory infection of 48% and an overall reduction in under five mortality of 32%.

The recommendations were originally designed for use in first level treatment facilities. Subsequently, they were used in community-based situations, with the guidelines implemented by community health workers rather than medical staff with 'higher' training. Sazawal and Black (2003) conducted a meta-analysis of nine community-based trials, and found that standard case management of ARI in the community by community health workers reduced overall mortality in children under five years by 24% and pneumonia-specific mortality in children under five years by 36% .

[3] A 'first level' facility is a facility at which a child can first gain access to health care provided by staff with formal health training, however basic.

1.5 Rationale for surveillance of *Streptococcus pneumoniae*

1.5.1 Epidemiology of *Streptococcus pneumoniae*

Wardlaw et al estimated that 21% of deaths in children under five in South Asia were caused by pneumonia, and probably in over half of these, *Streptococcus pneumoniae* was the causative organism (Wardlaw et al 2006, p5&7). Worldwide, pneumonia caused by *Streptococcus pneumoniae* may cause 1.5 million deaths a year in children under five years old. This is therefore an important organism.

Streptococcus pneumoniae is a capsulated Gram-positive bacterium commonly found in the nasopharynx of children, and less frequently in adults. The human nasopharynx is its natural reservoir, and apart from one serotype occasionally isolated from the nasopharynx of horses, it has no animal reservoir. It is usually a commensal organism. Occasionally *Streptococcus pneumoniae* is isolated from sites which are usually sterile, and in these sites it can cause disease. Most commonly, it causes pneumonia[4], but it can also cause meningitis and otitis media.

1.5.2 Carriage

Longitudinal studies in young children indicate a progressive rise in isolation rates from nasopharyngeal samples from less than 10% in the first few weeks of life, to nearly 100% at one year of age in some studies (Crook et al, in Tuomanen et al, 2004, p 138). The relationship between carriage and invasive disease is not well understood. Studies have tried to gain information on the duration of carriage in the nasopharynx after

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[4] Pneumonia is a respiratory disease characterized by inflammation of the lung parenchyma (excluding the bronchi) with congestion, caused by the multiplication of viruses, bacteria or other organisms at those sites, or by inhaled chemical irritants. Acute respiratory infection describes a group of diseases caused by infectious agents of the respiratory tract, including pneumonia, bronchitis and bronchiolitis. In practice terms, it is difficult to distinguish between the different types of acute respiratory infection without sophisticated diagnostic equipment.

acquisition. Gray et al followed 79 children from birth to two years of age; they estimated that serotypes 6, 14, 19, 23 were carried for 4 months, and other serotypes for 2.7 months (Gray et al, 1980). Smith et al in Papua New Guinea estimated that serotypes 6 and 19 were carried for 60 days, others for 12 days (Smith et al, 1993). Sleeman et al reported following two cohorts of children in the UK, one for six months and one for two years, and found that median carriage times between six and 22 weeks. This study also sought to calculate an 'attack-rate', and found that different serotypes had vastly different rates of invasion, from five to more than 50 cases per 100 000 acquisitions, and that attack rates seemed to be higher for serotypes with shorter carriage periods (Sleeman et al, 2002). This evidence shows that carriage of *Streptococcus pneumoniae* is episodic and age related, and that acquisition is followed by elimination, followed by reacquisition.

Carriage rates in other analagous studies

Table 1.1 has been compiled by the author, and shows rates of isolation of *Streptococcus pneumoniae* from nasopharyngeal swabs taken from children in 22 studies from around the world.

location	setting	no. children	age range (m)	isolation rate %
Hong Kong (1)	community, urban	1978	2 – 72	19
Taiwan (2)	well baby clinic	478	1 – 14	20
Taiwan (3)	community, urban	2905	2 – 84	21
Belgium (4)	community, urban	467	3 – 36	21
Eastern Europe (5)	hospital outpatient & day care centre	954	0 – 60	27
Australia (6)	community, urban	1267	6 – 54	29
Mexico (7)	community, urban	450	1 – 60	29
South Africa (8)	clinic	303	1 – 60	40
Fiji (9)	not stated	440	3 – 13	44
Vietnam (10)	community, urban and rural	911	12 – 184	44
USA (11)	rural	200	12 – 60	44
Canada (12)	community, urban	1322	0 – 60	44
Bangladesh (13)	community, urban and rural	2839	0 – 60	47
Indonesia (14)	community, urban and rural	484	0 – 25	48
Malawi (15)	not stated	200	0 – 60	48
India (16)	community, urban and rural	2400	60 – 120	53
Kazakhstan, Uzbekistan, Kirghizstan (17)	mixed, urban/rural, comm/hosp	630	2 – 59	59
Uganda (18)	community, urban	191	0 – 48	62
Botswana (19)	hospital inpatient and outpatient	187	2 – 60	69
Zambia (20)	outpatient at hospital	260	1 – 60	72
Central African Republic (21)	ill children hospital outpatient	371	not stated	73
Botswana (19)	hospital inpatient and outpatient	62	2 – 60	85

1 Chiu et al (2001)
2 Lo et al (2003)
3 Chiou et al (1998)
4 Malfroot et al (2004)
5 Applebaum et al (1996)
6 Hansman and Morris (1988)
7 Miranda-Novales et al (1997)
8 Huebner et al (2000)
9 Russell et al (2006)
10 Parry et al (2000)
11 Samore et al (2001)
12 Kellner and Ford-Jones (1999)
13 Saha et al. (2003)
14 Soewignjo et al (2001)
15 Yomo et al (1997)
16 Jain et al (2005)
17 Factor et al (2005)
18 Joloba et al (2001)
19 Huebner et al (1998)
20 Woolfson et al (1997)
21 Rowe et al (2000)

Table 1.1 Isolation rates of *Streptococcus pneumoniae* in various countries

These studies show that, in general, carriage of *Streptococcus pneumoniae* is higher in developing countries, particularly in Sub-Saharan Africa.

1.5.3 Antibiotic resistance

The first report of resistance in *Streptococcus pneumoniae* to an antibiotic used therapeutically was by Ross in 1939. Resistance to the then newly introduced sulfonamide 2-sulfanilylaminopyridene (sulfapyridene or M+B 693) was documented in a patient with meningitis, when isolates taken 3 days apart showed different susceptibilities, the first being fully susceptible, and the second showing considerably reduced susceptibility. The patient died despite having very high concentrations of the drug in his cerebro-spinal fluid.

The WHO's Global Strategy for Containment of Antibiotic Resistance, published in 2001 states that "antimicrobial use is the key driver of resistance. Paradoxically this selective pressure comes from a combination of overuse in many parts of the world, particularly for minor infections, misuse due to a lack of control measures and underuse due to lack of financial support to complete treatment courses" (WHO, 2001 (1)). This has been documented on both individual and community levels. Two studies, the first by Albrich et al published in 2004, and the second by Goossens et al published in 2005 calculated the correlation between communal antibiotic use and rates of resistance. Albrich et al examined penicillin and macrolide use and Goossens examined macrolides, penicillins, cephalosporins, quinolones and co-trimoxazole. Both found a close correlation between the defined daily dose per 1000 inhabitants and the percentage of non-susceptible organisms.

Antibiotic use has also been shown to increase carriage of resistant *Streptococcus pneumoniae* in individuals. In a community study in Iceland published in 1996, Arason et al took nasopharyngeal samples from 919 children under seven years old. *Streptococcus pneumoniae* was carried by 52.7% of the children, 9.7% of the isolates being resistant to penicillin. Children who had received antibiotics were significantly

more likely than other children to carry penicillin-resistant *Streptococcus pneumoniae*, especially if the treatment was recent; taking penicillin in the preceding two months gave an odds ratio of 6.75 for carriage of penicillin-resistant isolates, and an odds ratio of 6.0 if antibiotics were taken between three and 12 months before sampling. In a large retrospective analysis of 10350 isolates of *Streptococcus pneumoniae* in France, Bedos et al (1996) found that taking penicillin in the preceding six months gave an odds ratio of 1.9 for carriage of a penicillin-resistant isolate.

1.5.4 Experience of other analagous community health programmes in which workers with limited training distribute antibiotics

Considering the widespread use of the Integrated Management of Childhood Illness (IMCI) protocols (WHO 2001 (2)), and the evidence that these protocols can be effectively used by health workers with very limited training, it is surprising there is almost no published data on the effect on resistance of the distribution of antibiotics by such workers. Haines et al (2007), in their assessment of the effectiveness of using community health workers to deliver community management of common illness note the dearth of evidence and flag it up as a research priority.

The only study found in the literature was from Gilgit in north Pakistan, in which trained community health workers assessed and managed all pneumonia cases in children under five in the villages over the winter of 1992-3 (Rasmussen et al, 1994). This study is reported in an abstract for an international conference, which contained the barest details. Rasmussen was able to provide the author with an incomplete draft of the paper written, but not the primary data, which has been lost. Nasopharyngeal swab specimens were obtained from 341 patients with pneumonia; 241 of these swabs yielded *Streptococcus pneumoniae* or *Haemophilus influenzae* (56 *Haemophilus influenzae* alone, 114 *Streptococcus pneumoniae* alone, and 71 both). Isolates were

transported to a reference laboratory, where bacterial sensitivities were conducted. 157 isolates (66%) survived transport to the reference laboratory. 69% percent of these isolates had some degree of antimicrobial resistance, as tested by the disc-diffusion method (as described in section 2.4.5 below). A breakdown of susceptibilty by organism was not given.

1.5.5 Use of nasopharyngeal swabbing as a proxy for monitoring antibiotic susceptibility in disease-causing *Streptococcus pneumoniae*

Assessment of levels of antibiotic resistance in *Streptococcus pneumoniae* in community settings is made difficult by the fact that children when sick are usually diagnosed and managed at home. Hence they do not present to a facility where disease-causing organisms can be isolated from tissues in which they are causing disease. Thus, assessing whether wider antibiotic distribution leads to clinically relevant increases in resistance of *Streptococcus pneumoniae* to the antibiotics chosen for the case management guidelines is not possible by examining resistance patterns in disease-causing organisms directly.

In a comprehensive review article on the then-current research knowledge and initiatives on the pneumonia case-management initiatives, Rasmussen et al (2000) cite studies using nasopharyngeal sampling as a proxy for examination of disease-causing organisms.

Mastro et al (1993) conducted a study in and around the city of Rawalpindi in Pakistan. This study looked at 601 children who lived in the city, between 2 and 59 months of age admitted to hospital with ARI and 418 healthy controls (133 from an urban area, and 285 from a rural area). Nasopharyngeal swabs were taken from all children. *Streptococcus pneumoniae* was isolated from 387 (64%) of the children with acute

respiratory infection, 69 (52%) of urban healthy controls and 175 (61%) of rural healthy controls. Blood samples were taken from the children admitted to hospital. 216 (36%) of these blood samples were positive for a bacterial pathogen, of which 108 (50%) were *Streptococcus pneumoniae.* Isolates were sent to Denmark for capsular serotyping; 81/108 (75%) of the blood culture isolates and 457/631 (72%) nasopharyngeal isolates survived the transportation. There was 98% concordance between the serotype of an organism isolated in the blood and the nasopharyngeal isolate from the same child. Serotype concordance for blood culture isolates and nasopharyngeal isolates from children with acute respiratory infection were not significantly different, and reduced susceptibilty to penicillin, co-trimoxazole, chloramphenicol and erythromycin were not significantly different for blood culture isolates, nasopharyngeal isolates for children with acute respiratory infection and urban healthy controls, but were different for nasopharyngeal isolates from rural controls. The authors conclude that nasopharyngeal isolates obtained from children with ARI give a reasonable guide to the antibiotic susceptibility of invasive organisms.

Saha et al (2003) took nasopharyngeal swabs from 2248 children aged between 0-59m in Bangladesh, and compared the serotypes and antibiotic susceptibilty with 71 strains isolated from cerebrospinal fluid in children in the same age with meningitis. Serotype distribution was diverse and divergent, but rates of antibiotic susceptibility were not significantly different for penicillin, co-trimoxazole and erythromycin.

Kellner et al (1998) conducted a large study in Toronto, comparing the serotypes and antibiotic susceptibility of nasopharyngeal isolates from 1139 healthy children from 1 to 79 months of age in day care centres, taken between February 1995 and March 1996, and isolates from normally sterile sites in 96 ill children in January to December 1995. *Streptococcus pneumoniae* was isolated from nasopharyngeal swabs in 532 children (46%). The 13 most frequent serotypes represented in the two groups were the same,

except for 11A and 15A, which were isolated from children in the nasopharyngeal sample and not in the children with invasive disease. The rank order was, however, different in the two groups. Rates of antibiotic susceptibility were similar, although resistance to co-trimoxazole was significantly higher in the nasopharygngeal isolates.

Lehman et al 1997 reviewed data from studies of antibiotic susceptibility to penicillin in carriage and invasive strains of *Streptococcus pneumoniae* in the highlands of Papua New Guinea, both healthy subjects and those attending out-patient facilities with upper respiratory tract infections. There was a greater proportion of strains that had reduced susceptibility to penicillin than in most developing countries (87% of strains from the upper respiratory tract in one study had intermediate susceptibility to penicillin or were resistant). They found that invasive strains were more susceptible to penicillin than carriage strains. They concluded that carriage studies can provide accurate information on the serogroup distribution and susceptibility to penicillin of isolates of *Streptococcus pneumoniae* causing pneumonia, provided the serogroup distribution in the upper respiratory tract is similar to that of isolates causing pneumonia. In situations where the concordance between carriage and invasive strains is not so strong, then nasopharyngeal sampling may overestimate the proportion of isolates with reduced susceptibility to penicillin.

The literature suggests that examining the antibiotic susceptibility of isolates of *Streptococcus pneumoniae* obtained from nasopharyngeal swabs taken from children in the general population gives a conservative estimate of likely rates of susceptibility in invasive organisms.

1.5.6 Establishing a laboratory in similar situations to Wakhan

Only one account of the establishment of a diagnostic microbiology laboratory in a developing country could be found in the literature. Wain and Walsh (1994) wrote an account of setting up a diagnostic and research laboratory in Ho Chi Minh City in Vietnam. This laboratory was in an urban location. The main problems encountered were electricity supply, both in that the supply was occasionally intermittent, and of variable voltage. Maintaining a supply of deionised water was difficult due to low mains water pressure. All equipment and supplies had to be shipped from the UK, creating difficulties if the wrong item was ordered, or the wrong one sent or if anything was forgotten. If any equipment broke, it had to be fixed locally, as sending it back to the UK was very-time consuming, and usually very expensive. However, given all these difficulties, the authors ran an efficient laboratory service to culture common bacteria and test antibiotic sensitivity in that situation.

1.6 Summary

The published literature suggests that:

1. *Streptococcus pneumoniae* is an important cause of death from acute respiratory illness in children under five.

2. Health workers with limited training can use an algorithm to diagnose and effectively treat children with acute respiratory illness in the community.

3. Antibiotic usage leads to the susceptibility of the target bacteria to the antibiotic reducing over time.

4. Thus, an important research question needs to be answered: will the distribution of antibiotics to treat acute respiratory illness in children by health workers with very limited training lead to such levels of resistance that the antibiotic will become useless?

5. Examining the antibiotic susceptibility of isolates of *Streptococcus pneumoniae* from the nasopharynx of healthy children can give a conservative estimate of the susceptibility of disease-causing organisms to commonly used antibiotics.

6. It is possible to establish a laboratory in a remote area to culture common bacteria and test antibiotic sensitivity.

1.7 The hypothesis of this thesis

The hypothesis to be examined in this thesis is that

- comprehensive data on the health and living conditions of the population living in 28 communities in Wakhan district can be collected and analysed for use in the development of a community health programme;
- that within such a programme, illiterate women can be trained to follow a simple algorithm based on the WHO IMCI protcols to reduce deaths from acute respiratory infection, by treating dehydration and fever and providing co-trimoxazole to children with a fast breathing rate, and that by following such an algorithm, child mortality can be reduced;
- that a simple laboratory can be built and supplied in such a remote area, and a surveillance system for antibiotic resistance in nasopharyngeal isolates of *Streptococcus pneumoniae* from healthy children can be run,
- that the use of co-trimoxazole by health care workers with very limited training will lead to high rates of antibiotic resistance in *Streptococcus pneumoniae.*

2 Materials and Methods

2.1 Data collection - community and health data

The idea of examining antibiotic susceptibility in Wakhan as a research project emerged in the author's mind in 2002. Conversation with colleagues around the world led to the conclusion in the autumn of 2003 that such a project was possible. Funding was not obtained until April 2004. The aim of the survey work carried out in 2002 was to examine the health needs of the population of the eastern end of Wakhan District, and to use that data to design an appropriate community health programme. The survey data collected and programme design were not conceived with a view to publication, let alone in an academic thesis, and there are deficiencies in the nature and quality of the data collected. Nonetheless, the data have been collected as rigorously as possible, and represent the best data available for this remote region.

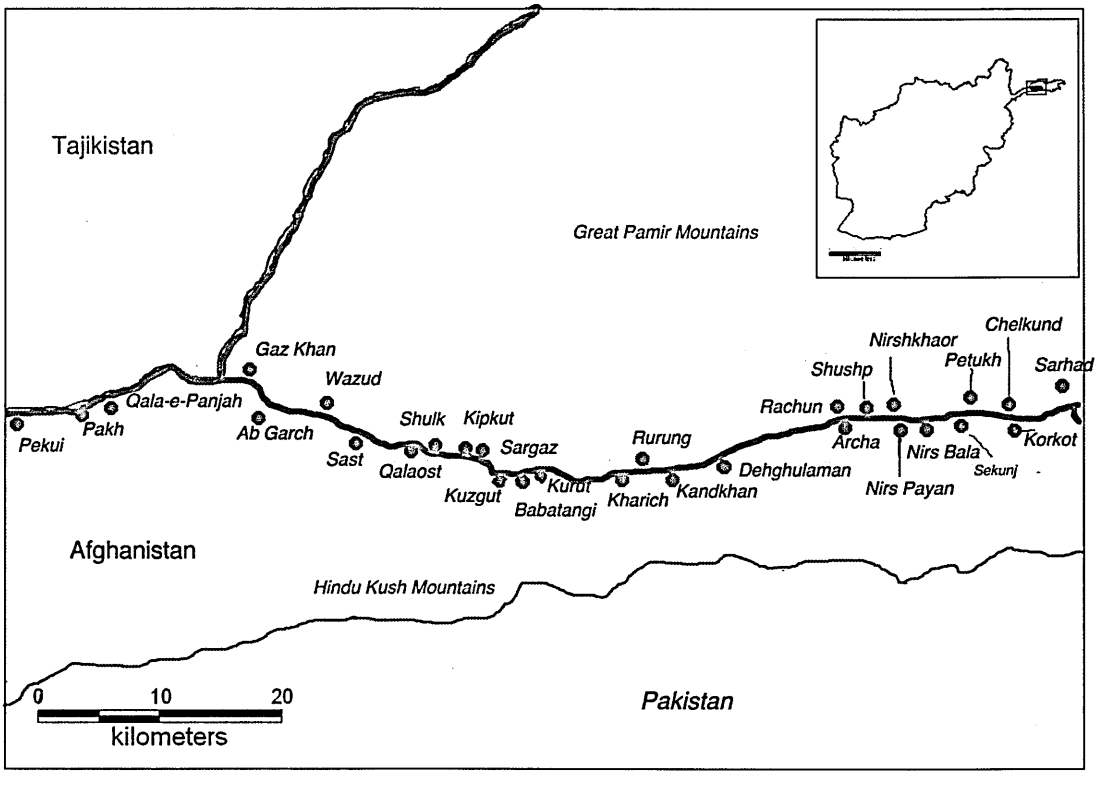
2.1.1 Initial reconnaissance, summer 2000

An initial reconnaissance was carried out for three weeks in August 2000. The aim of this trip was to get a general impression of the area, to establish some idea of the health needs and to investigate whether running a community health programme would be possible in this community. The author also met with workers from other NGOs in Faizabad, the provincial capital, to see what survey work or health work had been done in the district, collecting written reports, where available. These comprised brief reports from Focus (part of the Aga Khan Development Network) and Médecins Sans Frontières. From this initial reconnaisance,, it was clear that apart from sporadic vaccination campaigns (detailed in section 2.2.7 on p72) there was no health service provision and no regular work by any NGO in the upper part of Wakhan district.

2.1.2 2002 data collection

Subsequent survey work to examine the health needs in Wakhan was planned to start on 20th September 2001. However, all ex-patriates were evacuated from Afghanistan and North-West Pakistan in the week following the terrorist attacks in New York on 11th September 2001. The author did not return to Peshawar until June 2002, after which he travelled to Wakhan and the data collection started.

The survey was conducted in villages in the upper part of the cultivated area of Wakhan. The villages surveyed are shown in map 2.1.



Map 2.1 Map of villages in Wakan District surveyed in 2002, and then included in research programme

The aims of the survey

Discussions with the community during the reconnaissance in 2000, with data from other surveys from Afghan Aid, Médecins Sans Frontières and Focus (see 1.2.4. above) showed that there were probably significant health problems in Wakhan, no provision of preventative or curative health services, and that setting up and running a

community health programme was possible and could make an impact on child mortality. However, there were very few data about the rates of mortality and causes of death. The aim of the data collection in 2002 was to establish more formally the mortality rates in neonates, infants and children, to find out as far as possible the causes of child death and to gather information about the community which might directly or indirectly influence the child death rates.

The survey form

The survey form was designed by the author and Noreen Gillespie of Medair (a Swiss NGO providing health services) in March 2001. Medair were planning to conduct a similar survey in Ragh District in western Badakhshan in the summer of 2001, and Medair and ORA decided that a common form for both surveys would be most efficient. It was based on sample community survey forms published in a standard text used by many charities around the world working in community health (Lankester 2000). The form was written in English and then translated into Dari, one of the two national languages of Afghanistan, and the only one used in the north-east of the country. A set of notes explaining how the form should be filled in was also written in English and translated. The translation was checked for accuracy and comprehensibility by several Dari speakers before the final form went to press for the Medair survey. Medair then held a number of 'focus groups' to go through the form, and a few minor amendments, mainly simplifications, were made. After the Medair survey had been completed, ORA and Medair staff met to discuss further improvements, which were made.

A copy of the final version of the form, which was used in the ORA Wakhan Survey, and completion notes are attached in Appendices 1 and 2.

Definition of household

The main unit of the survey was 'the household'. A household was defined as the group of people who slept most nights in that particular building. In the vast majority of places, there was no controversy about who was and was not a member of the household. In two situations, one in Boroghil and one in Panja, it became apparent after completing the form that the people recorded as being in a single household slept in two separate buildings, and that there was no regular routine of who slept in which building. In both situations, the two houses were regarded as one household.

Selection of households

After surveying three houses in Boroghil as a 'pilot', the team decided that one in three houses should be surveyed. One in three would give a good representative sample, and yet not take too long to complete in each community, where resources for hospitality were strained already. On arrival in each community, two members of the team went around the community with a local person, visiting each household and chalking a number on the door. A map of the positions of the houses and their numbers was made. The number of houses in the community was divided by three, and the figure rounded up or down to the nearest whole number, e.g. if there were 13 houses, four should be selected for survey, and if there 14, then five should be selected for survey. The numbers of the houses on pre-prepared cards were put into a hat, and the correct number of cards were drawn 'blindly' by members of the survey team and local community. The houses with the corresponding numbers were surveyed. If there was no-one in the household to answer the questionnaire, then the next house numerically was surveyed.

In two places, Abgarch and Deghulaman, the houses were too spread out for the formal mapping and numbering process to be done (in both cases, it would have taken a full day to do it, and time was short). In these villages, the houses were divided into

clusters of between four and seven houses, and numbers drawn randomly from the hat for each cluster. In both places, the appropriate number of houses was selected.

Three very isolated communities, one of four houses and two of two houses were excluded from the survey as being too remote to reach easily. Ideally, two of these households should have been surveyed. One isolated household, part of Kuzgut, was drawn, but on arrival there three days later (accessing from the other side of the river), there was no-one at home. One household was drawn in the Deghulaman draw which was two hours' walk from the village in an easterly direction, on the way to the next community. On arriving there, it was discovered that someone had died in the household on the preceding day, and no-one would have been willing to take part in the survey. At that juncture, it was not feasible to turn back to the main village to select another household for survey.

Questioning

The survey team consisted of Fahim Ahmad Sultani (a male Dari-speaking Afghan from Kabul), Turob (a local male Afghan from the middle of the area being surveyed) and Eleanor or Alex Duncan. Fahim and Turob were given half a day's training about the form and principles of questioning. They were then closely observed by Alex Duncan for the first five households, and their technique refined. After that, either Alex or Eleanor Duncan (who both speak good Dari) monitored the process.

On arrival in a household, Turob would explain what the survey was and obtain permission to ask questions from the head of household. This person is usually the oldest male. In some households, if the oldest male was very old, his son would be regarded as the head of the household. In other situations, if a household was made up of the descendants of several brothers, and the oldest brother died, then his son

would take on the role of head of the household, even though he was younger than his uncle.

Turob would then explain the purpose of the survey and make it clear that the information gained was to be used only by ORA for project design, and would not be given to the government, the military or the Shah for purposes of taxation or any other reason. Fahim would then ask the questions, which Turob would translate into Wakhi if necessary. The answers would then be translated back into Dari, and recorded on the form. Usually the Dari form of the question was simplified for ease of translation. Occasional translation difficulties occurred. For example, there is no easy way of saying "in the past seven years" in Wakhi. However, it seemed that the translator was able to put across the questions in a way that people understood, but it was not possible to verify this. All the questions except the women's questions were usually answered by one main informant, usually the head of household if present. Often other members of the household were consulted, for example, mothers about vaccination of their children.

The first three questions concerned perceived problems in the area, both general and health problems, and opinions as to the causes of the health problems. The surveyors were specifically asked not to prompt the informants in any way. Others present from other households were also asked to stay quiet. Questions about health care, deaths and agriculture were asked, and details of each member of the household were recorded. Other members of the household were invited to debate the answers with the head of the household before the 'definitive' answer was recorded. When this section had been completed, all men were asked to leave the room, and Eleanor Duncan asked questions about child mortality, maternal mortality and weaning to women only, translated by Turob. The team had tried to find a female translator for these questions, but none was available – very few women speak adequate Dari.

A village elder would often accompany the team on the survey, although this was not encouraged. However, usually his presence was not regarded as a barrier to accurate information, and often he would help to clarify any problems faced.

2.1.3 Data analysis survey 2002

On return to Peshawar, a man was employed to enter the data from the forms written mainly in Dari into a Microsoft Access database. Forms written entirely in English were entered by Eleanor Duncan. After the data entry was completed, every database entry was rechecked by the author or Eleanor Duncan against the original form, and any data input errors were corrected. Analysis of the data was done by the author and Eleanor Duncan in Faizabad between December 2002 and March 2003 by extracting data in each category into Excel spreadsheets.

The population was stratified by age (in five year age bands) and sex. Each age band was compared by sex, using a *chi* squared 2x2 contingency table (http://statpages.org/ctab2x2.html).

Neonatal, child and infant mortalities were calculated by two methods. First, as a simple ratio by calculating rates from (number of deaths/number of births) multiplied by 1000 in the preceding seven years, giving a rate per 1000 live births. This approach assumes a 'steady state'. This means that both birth rate and death rate in the preceding seven years were presumed to be constant. The community did not report any anecdotal differences in the period, and there was very little change in health service provision. The only health interventions in the community during the period were very sporadic vaccination of young children (in a national polio campaign, and a

very low coverage level of diphtheria, pertussis and tetanus vaccination) and sporadic low level vaccination of women of child bearing age with tetanus toxoid, all reported in 3.1.2.5 below.

The second calculation was made by examining annual birth cohorts for each year and the deaths of children born in that year. Since precise dates of birth, ages and dates of death are unknown, then this in each cohort is an approximation. Rates for death under 28 days, under 12 months and under 24 months were calculated for each cohort, although for the 2000 and 2001 cohorts, the under 24 month rate could not be calculated, as a full 24 months had not elapsed, and for the 2001 and 2002 cohorts, only the under 28 day mortality rate could be calculated. Rates were calculated by (number of deaths/number of births) multiplied by 1000 in each annual cohort.

2.1.4 Data collection from 2003 onwards, and comparison with data from 1996-2002

The community training programme described in 2.2 below started in June 2003, and data on births and deaths was collected regularly from the women trained in each village. From November 2004, every time the village health workers were gathered for training, or, later in the programme, on each occasion a village was visited, the village health workers were questioned about births in the village in the preceding period, deaths in the village and the number of pregnant women. For births, the household, date, sex, outcome and whether colostrum was given was recorded. For deaths, household, approximate date, age, sex and probable cause of death were recorded. For pregnancies, parity, and a rough estimate of length of gestation to date were established. All these data were recorded in a register. The data was arranged in three cohorts (birth November 2004 - May 2006, June 2006 - May 2007 and June 2007 - May 2008).

A rate for deaths under 28 days was calculated by

(total no. deaths in children born 11.2004 - 5.2008) x 1000
(total no. of births in children born 11.2004 - 5.2008)

A rate for deaths under 12 month was calculated by

(total no. deaths in children born 11.2004 - 5.2007) x 1000
(total no. of births in children born 11.2004 - 5.2007)

A rate for deaths under 24 months was calculated by

(total no. deaths in children born 11.2004 - 5.2006) x 1000
(total no. of births in children born 11.2004 - 5.2006)

These rates were compared with rates of death in these three age groups for children born 1996-2002, using a *chi squared* 2 x 2 contingency table from http://statpages.org/ctab2x2.html

The cause of death was also tabulated, and compared for the two time periods, using a *chi squared* 2 x 2 contingency table from http://statpages.org/ctab2x2.html

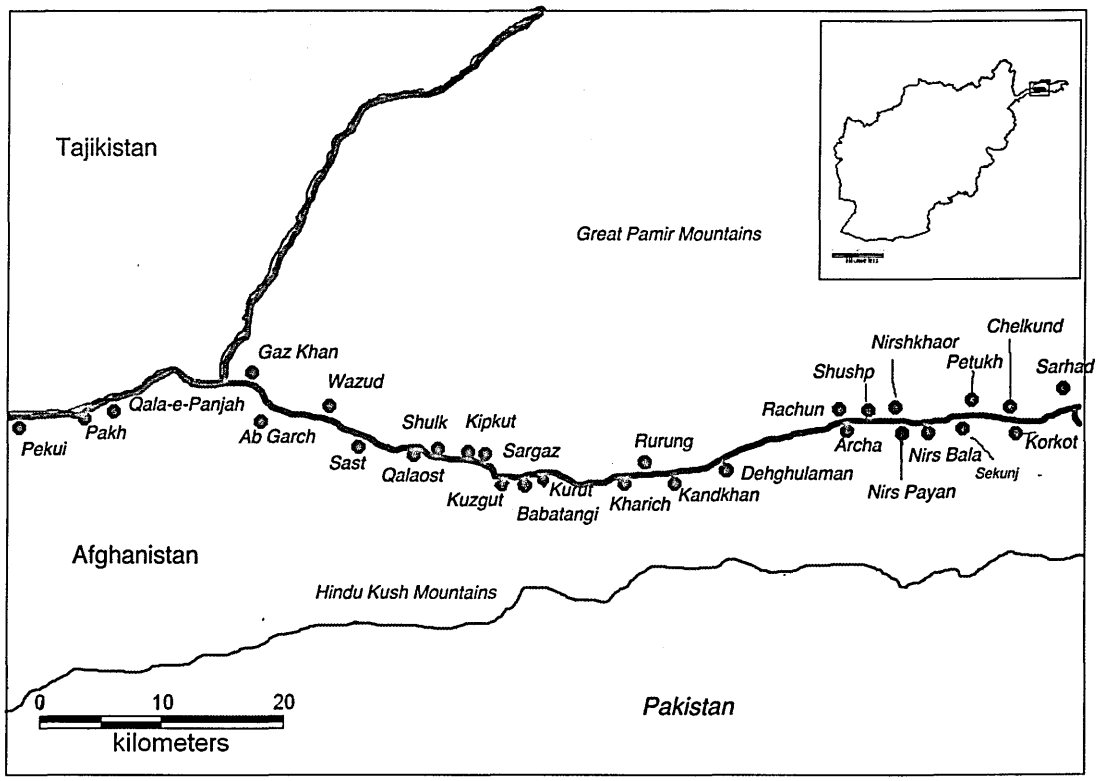
2.1.5 Collection of data concerning the physical and cultural geography of the area

Observations of the topography, climate and physical geography of the area were included in the report of the survey of 2002. Further observations of the culture and behaviour of the people of the area studied in Wakhan, including cultural attitudes to health and illness, illness behaviour and childbirth were made throughout the period 2003-2008 while the team was living in Wakhan. These observations are included in section 1.2.3 above.

2.2 Establishing the health project

The author set up this community health training programme in July 2003, on behalf of Orphans Refugees Aid (ORA). At first the project base was in Qala-e-Panja, towards

the western end of the area covered. In 2005, it moved to Kipkut in the middle of the area. Map 2.1 is reproduced to show the villages included in the programme.



Map 2.1 Map of villages in Wakan District surveyed in 2002

2.2.1 Designing the medical services

Analysis of the survey data (which will be discussed in detail in chapter 3.1.3) showed that the major objective of a health programme in this community should be to reduce child mortality. To do so community health training should focus on improving nutrition, and treating dehydration and acute respiratory illness (ARI). This was consistent with the situation and priorities in other analagous communities (section 1.3 above). The World Health Organisation Integrated Management of Childhood Illness protocols (WHO 2001 (2)) were adapted to the local situation for the training process.

Turob, a local man, who had helped on the survey in 2002 was employed to help with the training and supervision of the community health workers.

2.2.2 Selection of community health workers

ORA asked each community to select women to attend for health training. ORA asked that the women selected should be between 20 and 40 years of age, married with at least one child, and judged able to learn new ideas easily. The communities were asked to select one woman for every 20 households, i.e. if a village was 20 households or fewer, one woman should be trained, for 21-40 households, two women, for 41-59 households, three women etc. ORA did not require that the woman selected should be literate.

2.2.3 Training delivery - Phase One

Between June and October 2003, 45 women from 28 communities received 18 days' training in basic health education and treatment of simple illness. Only seven of these women had more than two years' schooling, and only one was functionally literate (able to take notes and read them back). The training was conducted in four venues to facilitate travel and accommodation of the women, and the training was conducted in four workshops each one month apart, so that the women were not away from home for more than two nights at a time. Each workshop had a major theme, and other minor themes were also included. The curriculum was as follows:

Major themes

Importance and benefits of giving colostrum (first milk) from soon after delivery.

Importance of introducing solid food from six months of age and no later, methods of introducing solid food and choice of appropriate foods for child growth.

Recognition, treatment and prevention of dehydration, using a home-made, cereal-based, oral rehydration solution, especially in relation to diarrhoea in young children.

Recognition and treatment of pneumonia in children (based on WHO IMCI Protocol).

Minor themes

Use of paracetamol for treating pain and fever in children and adults.

Use of antacids for treating indigestion problems in adults.

Recognition and treatment of gastrointestinal worms.

Use of iron and folate in pregnant women.

Treatment of wounds and burns.

Recognition and treatment of scabies.

Recognition of eye infections requiring antibiotic ointment.

Importance of vaccination (ORA was given direct responsibility for vaccination in 2007)

Reading basic numbers and using simplified dosage chart.

Basic care and nutrition of unwell children.

Eleanor Duncan conducted the training sessions on giving colostrum, the introduction of solid food from six months, and the use and preparation of cereal-based oral rehydration mixture. The author conducted all other training sessions.

The World Health Organisation Integrated Management of Childhood Illness (IMCI) Algorithm

IMCI is a system developed by the Child and Adolescent Health Unit of the World Health Organisation to improve and standardise the assessment and treatment of sick children in low level health facilities in the developing world. It is an algorithm that can be easily taught and followed by health staff with limited levels of education and medical training, and it has been widely implemented with some success in many parts of the world (WHO 2001 (2)).

The algorithm is as follows;

At each stage, the main symptoms and signs are discussed with the care giver who has brought the child, and action to be taken is outlined.

1. History taking – the trained health worker takes a detailed history from the child's carer.
2. General danger signs – the health worker looks for general danger signs of inability to drink, lethargy or diminished consciousness, vomiting or convulsions.
3. Assessment for cough or difficulty breathing.
4. Assessment for diarrhoea and dehydration.
5. Assessment for fever.
6. Assessment for ear problems.
7. Enquiry into immunization status.
8. Assessment of nutritional status.
9. Other problems.

The section on 'cough or difficulty breathing' is a research evidence-based protocol for the differentiation between pneumonia and simple cough or upper respiratory infection. Health workers are asked to assess respiratory rate. The protocol states that children under 12 months of age with a respiratory rate of more than 50 breaths a minute, and children between 12 and 59 months with a respiratory rate of more than 40 breaths a minute should receive antibiotic treatment. Those with chest in-drawing or stridor (difficult and noisy inspiration caused by an obstruction in the large upper airways) at rest should be given antibiotics and referred to hospital immediately.

The Wakhan *Sina Baghal* Algorithm

The WHO IMCI protocol was adapted by the author to what was known as "The Wakhan *Sina Baghal* Algorithm"

Any acute respiratory illness in small children in Wakhan is called *sina baghal*. This is a very non-specific term which literally means 'the embrace of the chest', and is used for colds, coughs and any other chest or breathing problem. In the training, we coined a new term, *sina baghal cherki* which means '*sina baghal* with muck or pus', and the protocol was designed to distinguish pneumonia needing antibiotic treatment from a simple illness only requiring conservative measures.

The protocol is as follows:

If the family says the child has *sina baghal*, the child must be removed from the *gaora*, or cradle.

Children up to two years of age are swaddled tightly and tied onto a wooden board in a cradle covered in a blanket, called a *gaora*. Not only is it more difficult for a child to cough efficiently in this position, but it also makes the family less aware of any changes in the child's condition. Removing the child from the *gaora* means they sit up, can cough more easily and receive a lot more attention.

The child should be assessed for dehydration.

The ORA team's experience in this community has shown that when a child is ill, they are often starved by their carers, who believe it is difficult, or even undesirable for them to eat or drink when ill. Children with *sina baghal* examined by the author were frequently significantly dehydrated.

The health workers should assess for dehydration by:

a. examining the child's tongue, to see if it is dry

b. looking for tears when the child cries

c. assessing skin turgor on the abdomen

d. asking about the amount of urine passed.

If any of these assessments are unsatisfactory, then the child should be actively rehydrated. If the child is still breast feeding, then very frequent feeds should be given. If not, then water, milk, soup and any liquid other than tea should be given. If the child has difficulty taking fluid, then they should be given fluid with a spoon from a cup every minute until they are able to drink themselves. If the signs of dehydration are still present a few hours later, a home-made cereal-based rehydration solution should be made up and given to the child. This consisted of four mugs of water (every household had the same chinese-made glass mugs, which were 250ml), two handfuls of flour and two 'two finger pinches' of salt, which were all boiled together and then cooled. A demonstration of how this should be made was given to the health workers in the training workshop, and they were instructed to demonstrate how to make the solution to women in the household of the sick child.

The child should be assessed for fever

If the child is hot then all but the lightest clothing should be removed; local custom in Wakhan requires children with fever to be wrapped up in many layers of clothes to make them sweat. If the child is very hot, then they should be sat in a bath of tepid water. The appropriate dose of paracetamol should be given.

After all this has been done, then:

The child's respiratory rate should be assessed.

Most people do not have watches, and those who do cannot read them. However, a pendulum 58cm long swings forward and back 40 times per minute, and a pendulum of 35cm swings at 50 per minute (see image 2.1).

Each health worker was given a stone of about 50g weight, with a string 58 cm long tied to it. A knot was tied at 35 cm. In a child of less than a year, they were instructed to hold the middle knot, and over one year, to hold the end of the string. While a second person counted the breaths the child took with a hand on the child's chest, the health worker counted 20 swings forward and back. (image 2.2) The number of breaths was then compared. If the child took more than 22 breaths, then they were judged to have fast breathing. The procedure should be repeated to confirm the rate. If the breathing rate was between 18 and 22, then the procedure should be repeated twice. A child with fast breathing was given co-trimoxazole tablets, to be ground up and given with 2ml of milk or water on a spoon.

The idea for using a pendulum came from a health worker in another organisation, and it was adapted and put into the algorithm by the author.

Image 2.1 The author demonstrates the pendulum

Image 2.2 A village health worker practises counting the pendulum beats.

Co-trimoxazole was chosen as the antibiotic distributed, as it is the one included in the New Emergency Health Kit as distributed by the International Dispensary Association

(IDA), based in Amsterdam. These kits are used in emergency situations all over the world. IDA's reasoning for using co-trimoxazole is that:

- Dosages are easy to learn; in pneumonia, any child between one and 12 years old receives one tablet of co-trimoxazole (400mg sulphamethoxazole, 80mg trimethoprim) twice a day for five days. A child under one year old receives half a tablet twice a day. In other conditions, co-trimoxazole is used at one quarter-tablet twice a day for two months to one year, half a tablet twice a day for one to five years and one tablet twice a day six -12 years.

- Co-trimoxazole has a long shelf-life.

- Co-trimoxazole does not have the problems of allergic reactions associated with penicillins.

As with all medication, co-trimoxazole can cause unwanted adverse effects. These include nausea, diarrhoea, headache, hyperkalaemia, skin rashes. Very rarely, it can cause the Stevens-Johnson syndrome, which is a severe and potentially fatal skin reaction, in which the layers of skin separate.

In between the training workshops, the author and his family lived in the area, being there for at least nine months of each year. In addition to the formal training, in the course of travelling within the area, members of the team saw sick patients with the health workers, and used these occasions as an opportunity to reinforce the training messages. Turob, the local training assistant, was well drilled in the materials we had taught, and also frequently reinforced the protocols.

2.2.4 Training delivery - Phase Two

In the summer of 2004, six training workshops were conducted. These consisted of thorough revision of all the topics from the previous summer, and some new training on 'hygienic delivery' of newborns. This training taught basic knowledge about pregnancy, childbirth and neonatal care, with guidelines for hygienic delivery to be taught to mothers, and when to seek help. The Government of Afghanistan did not allow village women to be trained as birth attendants, as their policy was to encourage women in labour to attend clinics where Government-registered staff were present to deliver. This is unrealistic in an area such as Wakhan, as the nearest facility for delivery was at least a day's journey away on foot, and no other transport is reliably available.

The use of simple 'home-made' delivery kits was also explained. These contained a plastic sheet 2m x 1m, a small piece of soap, a clean razor blade to cut the cord, two 15cm pieces of cotton tape to tie the cord and a piece of cotton cloth 75 x 75cm to wrap the baby (see Image 2.3). All of these materials were available in the bazaar in Ishkashem, the nearest small town 160km from the project base in Kipkut. Each kit cost just under US$1 to make. These were distributed to health workers each month according to how many she anticipated she might need, and always one in reserve. Initially, the author tried to collect 50 Afghanis ($1) for each kit in order to try to make the supply sustainable, but collecting the money was very difficult. In the end, it was decided to supply them free of charge, and attempt to obtain sufficient supplies of raw materials as part of the medicines budget.

Image 2.3 The delivery kit

A programme of family planning, known in Afghanistan for political reasons as 'family spacing' was also introduced at the request of the community, using depo-provera injections (a long-acting injectable progesterone contraceptive) every 12 weeks.

In Phase Two, the author conducted all the revision sessions of the Phase One topics, and sessions on pregnancy and childbirth were conducted by Eleanor Duncan and Dr Lucy Dakin, a British doctor who joined the team for six months in 2004.

2.2.5 Training delivery - Phase Three

In summer 2005, the author was not located in Wakhan, and Turob, the local training assistant travelled from village to village, again reinforcing nutrition, diarrhoea and acute respiratory infection protocols, and distributing supplies. The team returned to Wakhan in October 2005.

In 2006, during the five training training workshops, all previous topics were thoroughly reinforced, and the concept of growth monitoring introduced. In the workshops, the following principles of a growth monitoring programme were explained:

- Children failing to thrive are more likely to die from diarrhoea or respiratory disease.
- Detection of children failing to thrive can lead to better maternal feeding practice, improve growth and thus reduce mortality. Such children can also be examined for illness.
- Regular presentation for weighing reminds mothers of good child-feeding practice.
- Attendance for weighing gives opportunities for health education on other topics.
- Gathering for growth monitoring can be combined with immunisations and family planning injections, antenatal care (and distribution of delivery kits), and examination of sick people.

The growth chart and beam balance

As stated earlier, all but one of the health workers were functionally illiterate. A system of weighing and recording weights on a growth chart had to be devised which would be easy to use for people with no or very limited literacy skills. The author devised a system using a beam balance with a series of nylon bags of gravel, weighing 200g, 1kg and 5kg (see Image 2.4). 200g was chosen as the smallest increment because a girl growing on a rate equivalent to the mean growth velocity between the age of 12 and 36 months will gain around 200g per month. At younger ages, the growth velocity is higher.

The child was placed in nylon weighing 'trousers', and hung on one end of the beam. (Image 2.5). An identical nylon bag was hung on the other end, and the coloured bags added in a defined colour order. The hanging points were marked at each end by two 3cm nails, 1cm apart; the central point of this gap was equidistant from the centre of the beam, where a steel eye for hanging from a suitable point (usually a roof beam) was screwed into the beam. Before weighing started, the beam was balanced by means of putting small stones into the weight bags.

When the beam balanced, the child was removed and the bags laid out and compared with coloured bars on a growth chart adapted by the author from the UNICEF Afghanistan standard chart, which is not gender-specific (see Image 2.6). The position of the weight on the x-axis was established, and the child's age in months counted off up the y-axis. This is the reverse of the standard chart, but it was much easier to navigate through the coloured bars horizontally than vertically. The weight for age was plotted, and compared with previous weights (to establish growth velocity), and with marked centile lines (see Image 2.7).

Health workers were taught that if the child had a low weight for age, or was not growing, regardless of where they appeared on the centiles, the health worker should ask the mother about feeding (what they were feeding the child, how they did it, how much the child ate and how often). If the mother was generally feeding the child appropriately, then she was encouraged to continue. If the feeding practice was not appropriate, then the health worker would encourage the mother to adopt better practice. The health workers were trained to do this in a gentle and non-judgmental way.

Image 2.4 The beam balance

Image 2.5 The sand bags. The 200g blue bag had been lost the day before this photograph was taken, and replaced with 2 stones weighing 200g,held together with blue tape.

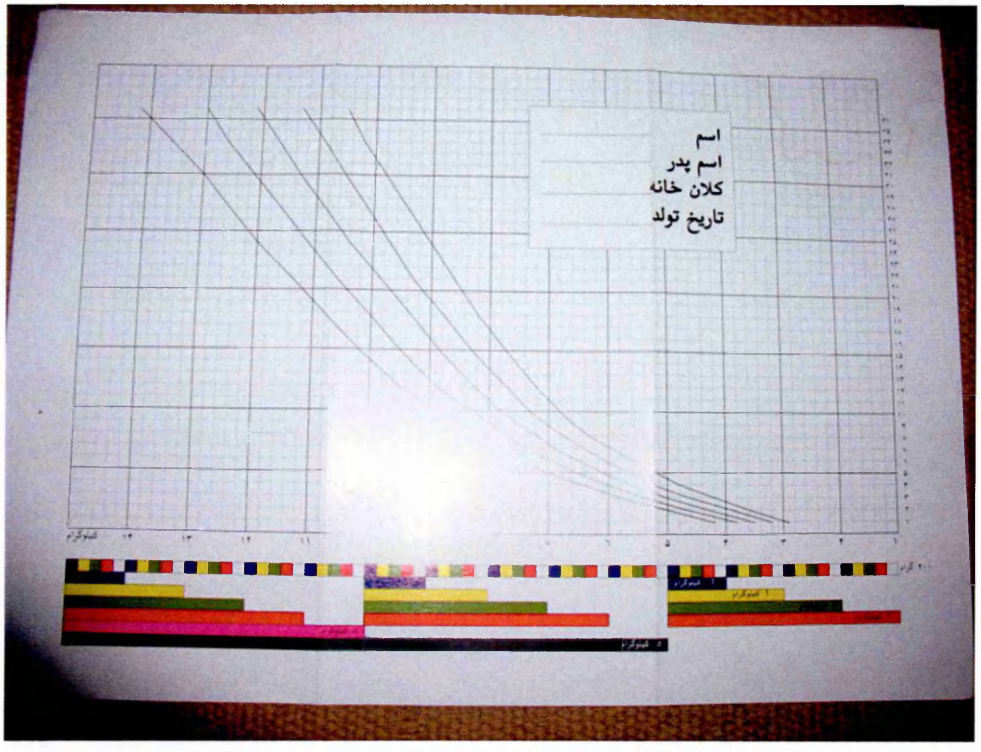


Image 2.6 The growth chart. The *y* axis on the right is age in months, and the *x* axis shows weight in kg

Image 2.7 Plotting the weight on the chart.

The accuracy of the scales was checked using weights from a commercial pan balance, and also occasionally the child in the weighing trousers was taken off the beam balance and hung on a Salter-style spring balance provided by UNICEF to check the weighing technique.

Clearly, to examine weight-for-age accurately, the child's date of birth must be established. This is not straightforward in a culture in which birthdays are not recorded. When the weighing programme started in April 2007, the author and Eleanor Duncan worked hard together to establish the month of birth of each child. In general for children under six months, this was relatively straightforward. For children between six months and three years (the upper limit of weighing), it was much harder. However, close questioning usually revealed a consensus about the season of birth, and even the stage of the season (i.e. barley sowing, wheat harvest, new year) etc. For most children, their date of birth could be established within three months, and often more accurately for younger children. Obviously as the programme matured children entered in the first month of life, so establishing age was no longer a problem.

Advantages and disadvantages of home-made scales

Using a home-made weighing and recording system had clear advantages and disadvantages.

Disadvantages

Since the smallest weight was 200g, the weight of the child could not be established to anything closer than 200g.

Occasionally the health worker would forget to balance the beam before starting (although this was a matter of up to 50g either way).

If the weight bags were selected in the wrong order, then plotting the weight accurately would be very difficult.

Calibration needs to be regular and thorough.

Bags of gravel occasionally leak, and 200g bags especially could be lost.

Advantages

Making the scales cost less than $1.50.

A Salter-type scale is easily broken if it is dropped. In such a remote area, obtaining a replacement is difficult. The beam balance was robust, and apart from gravel leakage, did not break.

The scales could be read and the weights plotted by workers with very little formal education.

Culturally, in Wakhan people were very familiar with beam balances, but not with spring balances.

A struggling child causes a lot of bounce on a spring balance, making it difficult to read. This is less of a problem with a beam balance.

2.2.6 Supplementary feeding and fertiliser distribution

From the 2002 survey it became clear that supplementary feeding of children from six months of age was an important issue. The lack of appropriate foodstuffs became more apparent during the first year of training. Following discussion with the ORA leadership in Kabul, and the raising of appropriate funding, in November 2003, November 2004 and November 2005, the Wakhan Community health project made a distribution of a 'superflour' to all children from six months to five years.

Superflour is a mixture of three flours, two from grains and one from a legume, mixed in equal quantities. The superflour initially used in Wakhan was produced by a charity in Kabul. They used one-third maize flour, one third rice flour and one-third gram flour (from chickpeas). The whole grains and peas were dry-roasted (to make the resulting mixture more tasty and lighter in texture) and then ground. A powdered mixture of vitamins A, D and B complex, iron and folic acid was added. (The project manufacturing this superflour has subsequently closed, so it has not been possible to establish the exact composition).

3 kg of superflour was distributed to households for all children from six months to five years of age for five months from November to March. This provided approximately 360 kilo-calories, 18 g of protein, and 6g of fat per day. (These figures are taken from the World Food Programme Emergency Field Operations Pocketbook, and refer to a commercial product of very similar constitution (WFP (2002), p160)). Mothers were taught how to prepare a soft porridge from this, adding oil if it was available in the household. Up to about 15 months of age, this diet, along with breast-feeding, provided all the child's nutritional needs (Savage-King, F., and Burgess, A., 1993 p137). Parents were taught that older children needed to eat family meals as well as eating superflour porridge.

Since such a distribution was evidently unsustainable in the long term, in 2006, a different tactic was adopted to improve weaning practice and infant feeding. In April 2006 and April 2007, 50 kg of fertiliser, (25kg urea and 25kg di-ammonium phosphate) was distributed to each household. This is the quantity that would normally be spread on one fifth of a hectare of land (one *jerib* by the Afghan measurement of area) according to Afghan Government recommendations. Local farmers reckoned that application of fertiliser would increase the yield of wheat by between 70 and 200%. One *jerib* is sown with 35kg of seed. Good soil and good weather may yield 120kg of

wheat, or poor soil and weather, 70kg. With fertiliser, this yield may exceed 200kg. In co-ordination with the village councils, each village collected 25 kg of wheat and 25 kg of peas from each farmer receiving fertiliser, which was stored in a community food bank, and distributed to each child from 6 months to 5 years at 2 kg of each per month for 6 months. From this, the household would make a home made superflour-like porridge, using the wheat/pea flour provided, with an equal third portion of millet flour, if it was available, or wheat flour if not. Although this flour was not enriched, it provided an equivalent amount of calories and protein. In addition to this, the surplus to the household of the increased yield over and above the 25kg wheat donated to the community food bank helped to improve food security in the household.

The author of this thesis supervised both these programmes.

2.2.7 Vaccination

In 2002, at the time of the survey conducted by ORA, vaccinatons were the direct responsibility of the MInistry of Public Health, with some technical support from WHO and UNICEF. Vaccinations had been administered by mobile teams from the Ministry of Public Health travelling into Wakhan on a sporadically, aided occasionally by staff from FOCUS, a relief organisation in the Aga Khan Development Network. The only consistent programme was the national campaign for polio eradication, which ran relatively well organised national immunisation days. Polio is an oral vaccine, and lay people, such as school teachers, can be trained to administer it, so coverage tends to much better than other vaccines requiring injection everywhere where such campaigns are run.

In 2004, vaccination in the whole of Wakhan District became the responsibility of Aga Khan Health Services. The polio campaigns improved, but coverage of other

vaccinations did not improve at all, except in the two villages at the very far estern end of the area of operation. Every time ORA discussed these issues with AKHS, improved geographical coverage was promised, but did not materialise. From the autumn of 2006, ORA started to lobby AKHS hard to allow ORA to take responsibility for vaccination in the area of operation of the ORA project under the 'light supervision' of AKHS, and in January 2007, two men travelled from Wakhan to Kabul at ORA's expense to undergo training as vaccinators. In March 2007, ORA signed a contract with AKHS and the MInistry of Public Health to provide all vaccinations under the Government Expanded Programme of Vaccination in the villages in which the ORA Wakhan Community Health Programme operated, and to the Kirghiz nomads in the high Pamir mountains above the main Wakhan valley. The author of this thesis supervised this programme.

2.2.8 Community attitude to the training programme and the retention of community health workers

The community was supportive and appreciative of the training programme. The heads of village councils expressed their appreciation of the programme to the author and also sent a communal letter, signed by all the village heads, to the District Administrator in Khandud, commending the work.

There was some change in personnel. Six communities requested that the women originally selected for training be replaced by new choices, and in one village, a woman chosen in this 'second wave' was also 'sacked' by the community. In all of these cases, the problem seemed to be a poor attitude rather than poor performance. In the third year, one health worker got married and moved village; the village into which she moved had two health workers selected in the 'second wave'. One of these women seemed to the author to be unable to go through the 'sina baghal protocol' adequately, and was considerably older than the upper age limit of around 40 that had been

suggested. The community was unhappy about her attitude too, so the newly-wed took her place. The village from which she had come selected a new health worker. One health worker died and was replaced, and a village that had not originally been part of the programme requested to be included, and selected two health workers, one of which was subsequently replaced.

When a new health worker was selected, a 'catch-up' course was arranged to cover the material already taught. Each seminar also contained a considerable amount of revision and reiteration of the core material, so it was not difficult for those who were not selected at the start of the programme to reach the same standard as those who had been selected initially.

2.2.9 Evaluation of the training

Evaluation through formal testing of the performance of the community health workers in following the protocols taught was not attempted with this group. The author received feedback from both the community health workers themselves and the communities they served. Approximately two thirds of the health workers trained were able to follow the '*sina baghal* protocol' reliably without prompting when questioned informally. Whether they really did follow the protocol when asked to see a child with *sina baghal* is less easy to assess. Given this uncertainty, it is more likely that co-trimoxazole was over-prescribed than under-prescribed by community health workers. However, the author's anecdotal experience is that anyone presenting with a runny nose to an Afghan doctor or a pharmacist in rural Badakhshan is sold co-trimoxazole (and frequently an inadequate course). Thus any protocol is better than none, and some over-prescription is probably better than child death.

The ultimate evaluation of the whole programme is in the measurement of mortality. Mortality rates for the period before 2002, and rates from data collected from November 2004 were compared. p values were calculated using a chi squared test, using an internet based calculator at http://statpages.org/ctab2x2.html

The actual contribution of the work of the community health workers to those figures is not possible to measure. However, given that the author personally treated very few children with pneumonia during the period of data collection, the contribution of the community health workers is likely to be a significant factor in the reduction of child mortality, which is described in section 3.2.1 below.

It would have been ideal to have compared the mortality in the area in which the project operated with a control area in which there was no change in health service provision. This would have been politically very difficult, in that it is unlikely that the project would have got permission to collect data in an area in which no training was done. There was a lot of pressure from the local authorities to extend the area of operation down the valley, to the west of the area of operation, but ORA did not feel that it was able to do this, since the distances were very large and the team would have become overstretched. Communities to the west of the area of operation also had easier access to health facilities in Ishkashem, at the western end of Wakhan District, as there was more transport available between Ishkashem and Khandud, the district administrative centre. Khandud was 15 km west of the last village included in the ORA programme.

In similar circumstances, evaluation of projects aimed at reducing death from acute respiratory infection have used death from another cause, such as diarrhoea, as a control. In this programme this was not deemed possible, as non-epidemic diarrhoea was a relatively uncommon cause of death compared with acute respiratory infection,

and the training for the community health workers included treatment of dehydration, to be applied to both ARI and diarrhoea.

2.3 Establishment of an antibiotic susceptibility surveillance system

The emergence of resistance to antibiotics in an area with little antibiotic exposure as an unwanted consequence of over-prescription of antibiotics by community health workers with very limited training, along with the possibility of a research programme to measure the emergence of reduced antibiotic susceptibility in *Streptococcus pneumoniae,* was first considered in 2002. At the time, the author was not able to find any data about similar research programmes with analagous populations, or any population served by a community health programme like the one envisaged in outline in Wakhan. Also, there was no laboratory anywhere in Afghanistan doing culture and sensitivity of common bacterial pathogens. If such data were to be obtained, it was clear that the author would have to set up the laboratory and do the work himself.

2.3.1 Obtaining funding

Funding to build the laboratory and for the equipment and reagents to run the programme was sought from numerous sources. After 15 months of trying, funding was secured from Lord Sainsbury of Turville in April 2004.

2.3.2 Obtaining permission and ethical approval

Permission to collect nasopharyngeal samples from children, and to run a small research microbiology laboratory was sought and obtained from the Ministry of Health of the Government of the Islamic Republic of Afghanistan, both at the national level, in Kabul, and at the provincial level, in Faizabad, Badakhshan Province.

Proposal submissions were made to the Open University Research Ethics Committee and the Government of the Islamic Republic of Afghanistan, Ministry of Health Medical Research Ethics Committee.

Issues of informed consent are discussed in section 3.4 below.

2.3.3 Constructing the laboratory facility

A two-roomed laboratory was constructed in a field next to the medical project base in Kipkut.

The walls were made from rocks and mud, and the project supplied the roofing beams, plywood to line the ceiling, doors, window frames and glass and skylight frame and glass. Each room was 3m x 3m.

An approximate floor plan is below in Figure 2.1, and Image 2.8 shows the building from outside.

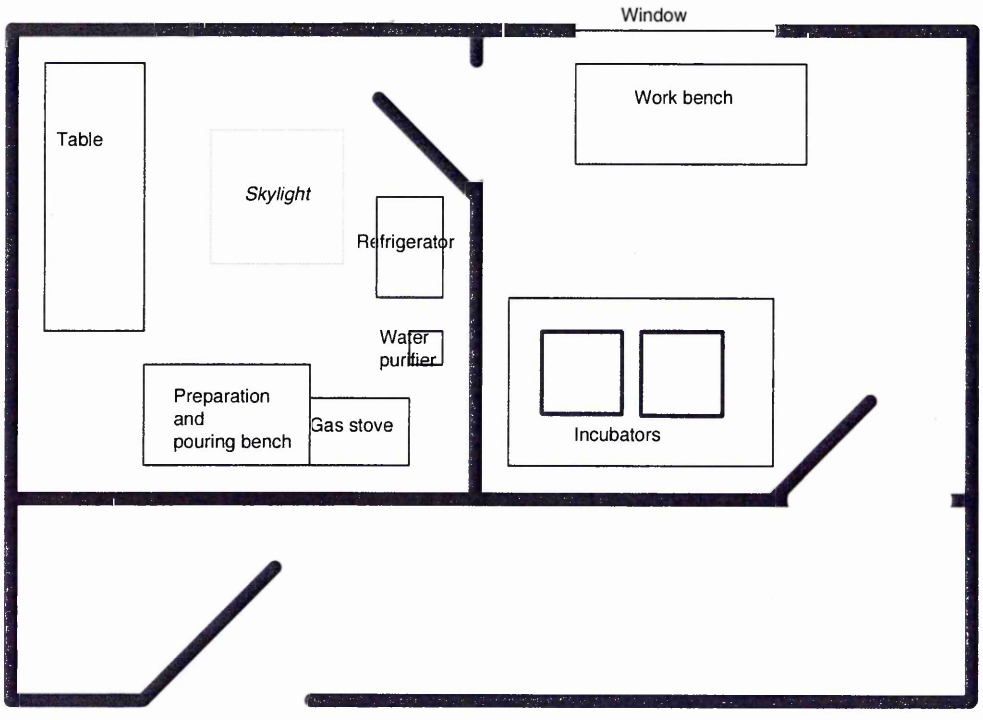


Figure 2.1 Floor plan of laboratory building

Image 2.8 The laboratory building (left). The ibex horns over the door are a local custom.

Power supply

Power was provided by ten 70w 12v solar panels (BP Tata, India), and two 24v wind turbines (manufactured by Bergey, USA).

The wind turbines were mounted on 6m pylons, made in Kabul from box steel and transported in sections. The pylons were raised using a hand winch and a gin pole. Image 2.9 shows the turbines erected.

Image 2.9 The wind turbines

Image 2.10 The solar panels. The black wires in the foreground are from the turbines.

The solar panels were connected in series into five pairs, and then the pairs in parallel.

Each wind turbine had a control box to which it was connected, and the solar panels were connected into one of these boxes. Both boxes connected to an array of twenty 12 Volt deep cycle lead acid 90 Amp-hour batteries, which were connected in pairs, and the 10 pairs connected in parallel. These were connected to the output of the control boxes, which were then connected to a 24-to-12 Volt converter, which was connected to two 150 Amp-hour lead acid truck batteries connected in parallel, in turn connected to the incubators via a 12vDC/240vAC inverter (the black box seen on top of the left incubator in Image 2.11 below). The truck batteries buffered the surge when the incubator element switched on. Lighting was run from the 12V DC supply.

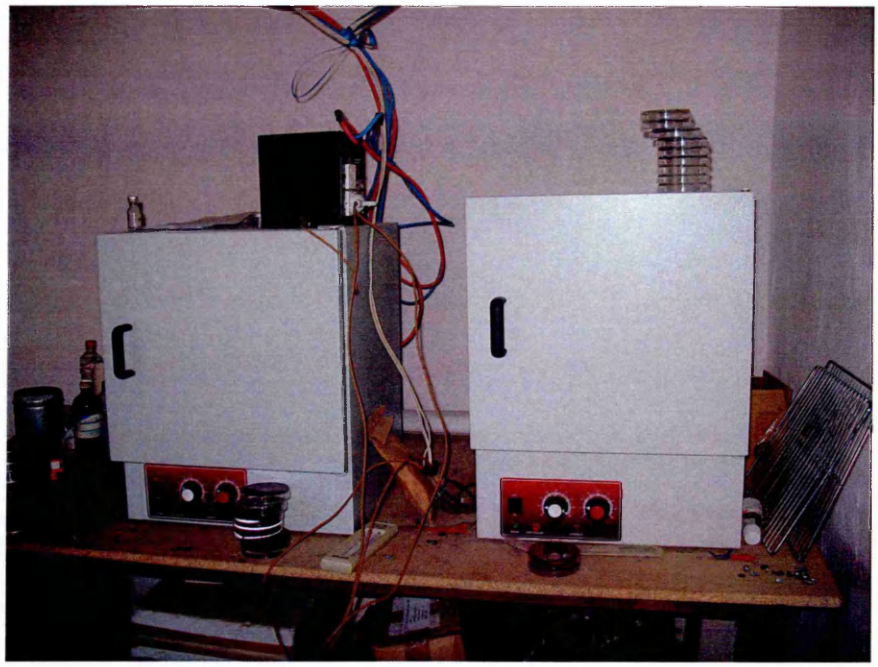


Image 2.11 Genlab Incubators.

Water supply

The water brought by the donkey was stored in the blue plastic barrel seen in the corner of Image 2.12 below. The particulates were removed in the two-bucket ceramic candle filter (Britsh Berkfeld) on top of the red stool, and then dripped through the deionising column (A.J. Cope) into the 20 litre container below.

Image 2.12 Water supply (for description, see text)

2.3.4 Equipping the laboratory, establishing the supply chain and communications

Non-consumable supplies

As much as possible of these were purchased at Standard Supplies Medical and Scientific Equipment Store, Khyber Bazaar, Peshawar, Pakistan, and transported by road to Kabul.

Equipment not available there was purchased from A.J. Cope Ltd in Hackney, London E3, and air-freighted to Kabul. The equipment was securely packed and sent by truck to Kipkut, a journey of four days.

Media, reagents and sensitivity testing supplies

These were sent from the Sanger Institute in Hinxton, Cambridge, via the British Forces Post Office, to a Royal Army Medical Corps contact in Kabul, from where they were collected and stored at the ORA office in Kabul. These were sent by truck to Kipkut. This was done in the winter, as the rivers were lower and often frozen, so the roads were easier. However, since the road crossed a pass 3500m high, some of the reagents froze. In December 2007, the truck broke down at an altitude of 2700m, and was stuck for 12 days. At that altitude, the night-time temperature at that time of year was below minus 15° centigrade. Egg tellurite additive for use in identifying *Staphylococcus aureus* was frozen and therefore useless, so a surveillance project for that organism had to be abandoned.

Communications

Communications were via a Thuraya satellite telephone until March 2007, after which a satellite internet system was installed.

2.3.5 Preparing media, including a source of sheep blood

In the UK, almost all the media used for this project would be purchased as ready-poured plates. It was not practicable to import such plates to Wakhan, so other arrangements for preparation of media, including the collection of blood, had to be made.

Sheep blood was required for media preparation, and this was obtained from local animals. The blood was collected in 300ml flat glass bottles, with a sheet rubber top (from a car inner tube held in place with wire), and glass beads for defibrination. The rubber top was covered in aluminium foil to maintain the sterility of the rubber surface. The bottles were autoclaved.

The sheep was held head down by an assistant on the back of the project pick-up truck. The area over the jugular vein was shaved with a scalpel blade, and then the skin cleaned with cetrimide 15% + chlorhexidine gluconate 1.5% solution, diluted 5:1. A 1cm incision was made in the skin over the vein, and a wide-bore (16G) cannula inserted into the vein. The cannula was connected to a 50ml syringe through a three-way tap. The side branch was connnected to a wide-bore needle, which was pushed through the rubber sheet covering the neck of the sterilised bottle. 200ml of blood was put into each bottle, which was oscillated gently, the fibrin adhering to the glass beads. This is shown in Images 2.13 - 2.17. The blood was strained using a sterilised tea-strainer into sterile bottles and stored at 4° Centigrade.

Image 2.13 The sheep was secured head down in the back of the pick-up.

Image 2.14 The jugular area was cleaned with cetrimide 15% + chlorhexidine gluconate 1.5%, diluted 5:1.

Image 2.15 The jugular area was shaved.

Image 2.16 A 16 G canula was inserted and connected to a 50ml syringe, a three-way tap and line from a blood-giving set.

Image 2.17 200ml of blood was transferred into a 300ml flat bottle containing glass beads and capped with a rubber sheet.

Media were prepared in the laboratory from dried media (all from Oxoid, UK) and were prepared according to the manufacturer's instructions with de-ionised water, and decanted in 200ml aliquots into 300ml flat bottles. These were then sterilised in the stove-top pressure-cooker type autoclave shown in Image 2.18.

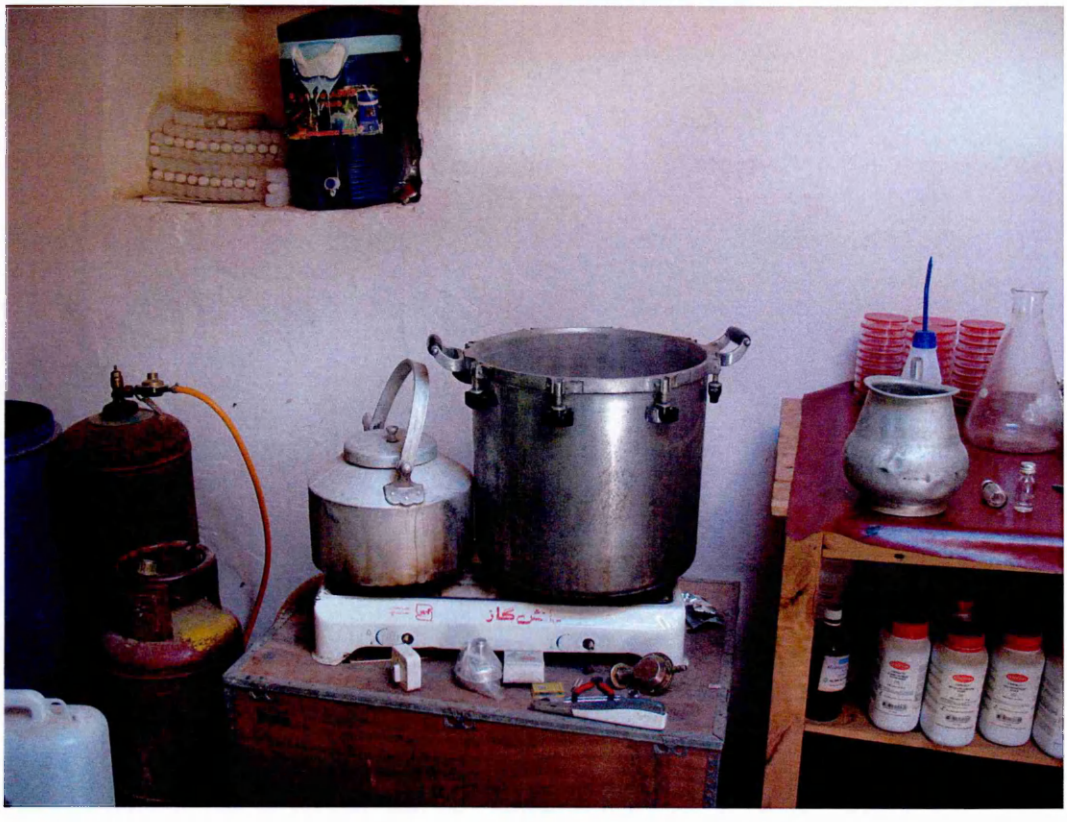


Image 2.18 Dried media (bottom right) and autoclave

Because of the altitude, media were sterilised for 24 minutes. The autoclave was allowed to cool until pressure was equalised, and the bottles were placed in boiling water to the level of the medium in an insulated box (a standard picnic 'cool box'), which cooled slowly to 50° Centigrade. Sheep blood, and if required, crystal violet solution were then added with a pipette.

Crystal violet to a concentration of 1 in 50 000 was added to the sheep blood agar to inhibit Staphylococcal growth, for use in the isolation of *Streptococcus pneumoniae*.

The media were poured to a 4mm depth in 90mm petri dishes, allowed to cool, labelled, and then refrigerated. The author is seen pouring plates in Image 2.19.

Image 2.19 The media were then poured to a 4mm depth in 90mm petri dishes, allowed to cool, and labelled.

In 2005 and 2006-7, glass petri dishes were used, and then washed and resterilised, the used agar being sterilised and buried. In 2008, since a very large number of samples had to be processed in a very short time, disposable petri dishes were used and incinerated after use.

2.3.6 Difficulties in setting up and running a laboratory in Wakhan

Altitude

The altitude of 3027m made power production difficult in that although the 24V turbines were nominally rated as 1000W turbines, at this altitude they did not produce more than 600W even in a strong wind.

The reduced oxygen tension also made the use of a standard bunsen burner impossible, as with the butane available, even with the hole in the collar fully open, it burned with a yellow flame. A spirit burner was used instead.

High altitude is also associated with low temperatures, as discussed below.

Topography

The laboratory was situated in a deep valley, and in the middle of the winter, the sun dipped behind the mountains at 1.15 pm. The combination of this and the altitude as mentioned above made maintaining adequate power to the incubators difficult.

Temperature

In the middle of the winter, night-time temperatures dropped below minus 20° Centigrade. It was difficult to prevent everything in the laboratory freezing, and a gas fire had to be left on very low overnight. Even with a gas fire running on full, the temperature in the laboratory was around 5° Centigrade. As *Streptococcus pneumoniae* is sensitive to cold, this meant that the plates had to be taken from the incubator a few at a time and placed on top of a hot water bottle on the bench, and covered in a blanket to prevent them from cooling too much.

Remoteness

Kipkut village, where the laboratory was situated, was 15 hours' drive from Faizabad, the nearest significant town, which was then two days' journey from Kabul. Transporting equipment and supplies over this distance was challenging, especially since the road was very rough, and fragile equipment had to be very well packed to prevent it breaking. The journey was also very expensive - hiring a truck cost US $2000, and the project could only afford to pay for this three times a year. The route to Kabul crosses the Salang Pass, through a tunnel at 3400m. In December 2007, the truck bringing supplies broke down just below the tunnel, and was stuck for twelve days. All the supplies on the truck froze, and some of the reagents were spoiled and thus unusable.

Towards the end of the first collection period in January 2007, one of the incubators overheated, and further investigation revealed that the thermostat was faulty. In the UK, it would have been an easy task to return the incubator to the manufacturer for repair. However, in the circumstances, this was not possible, and getting a replacement thermostat took four months, and the author needed to fit himself, following instructions from the manufacturer.

Lack of utilities supply

Issues concerning power supplies have been described above. Gas for heating and running the autoclaves had to be brought in 25kg cannisters. Most of these came from Iran and were of poor quality. The head valves on the cannisters sometimes leaked when shut, and sometimes leaked around the edges when the supply regulator was attached. Two cannisters arrived full, but the valves could not be opened at all.

Water was awkward to obtain. The deionising column was designed to be attached to a high pressure mains water supply, which forced water from the bottom up through the

column, the supply being controlled by a tap on the top of the column. This arrangement was designed to supply five litres a minute on demand. In the Kipkut laboratory, the column had to be turned upside-down, and water dripped through. Maximum supply was about 30 litres per day.

Supply chain

Many basic supplies for equipping the laboratory were purchased in the Khyber Bazaar, Peshawar, Pakistan. These had to be transported over the border to Kabul and thence up to Kipkut. Equipment not available in Peshawar, and all media and reagents had to be ordered from the UK.

Customs procedures for importing equipment into Afghanistan are convoluted. The initial shipment came by airfreight, and it required five visits to the airport, and collection of permission letters and signatures from three Government ministries to get the shipment cleared through customs. One incubator is still in the Kabul customs yard, as permission for import could not be obtained.

One shipment of supplies did not arrive in Kabul in time to be transported to Kipkut on the supply truck, even though the truck was delayed to wait for it. However, since medicines were needed urgently for the winter season, the truck had to leave Kabul without it, and an alternative arrangement, described in section 2.5.8, had to be made.

Subsequent shipments of consumable supplies were sent to a contact in the Royal Army Medical Corps, via the British Forces Post Office to the main UK Army base in Kabul. This route bypassed customs. It proved to be the cheapest and most reliable route for supplies. However, no parcel bigger than a shoe box could be transported this way, so all the supplies had to be packaged in small quantities, which was rather time - consuming.

Security

Security is always an issue to be considered in Afghanistan. The area around Kipkut was quiet and peaceful. However, the road from Kipkut to Faizabad passed through an area of heavy opium poppy cultivation, where security was at times precarious. This made travel difficult. In November 2007, an NGO vehicle was ambushed and two workers murdered. The ORA leadership in Kabul decided that it would be best for non-Afghans to avoid that road for a period. At the time of the murder, the team was in the UK for a break, and therefore had to return to Kipkut on a longer route via Tajikistan, a detour of three days. However, the project car was at the airport in Faizabad. The truck bringing the winter supplies, already late after breaking down at the Salang Pass, had to load the car in Faizabad, and bring it up to Kipkut covered in a tarpaulin. All project work over that period whilst awaiting the car had to be done on foot with a donkey for the equipment. Although the security situation never directly curtailed the work, the potential vulnerability of the project in the generally unstable national situation often made planning complicated.

2.4 Bacteriology methods

All laboratory procedures were conducted in accordance with the Clinical and Laboratory Standards Institute Performance Standards for Antimicrobial Susceptibility Testing; Fifteenth Informational Supplement (2005).

2.4.1 Sample collection

Nasopharyngeal samples for the isolation of *Streoptococcus pneumoniae* were collected in three batches:

November 2005 - January 2006	60 samples
November 2006 – January 2007	192 samples
April 2008	239 samples

Participant selection

The aim was to collect nasopharyngeal samples from each household, from a child aged between 12 and 23 months, or as near to that age as possible.

In the batches taken 2006 – 7, collections were made at a central place in each village, usually the guest room of the chairman of the village council. He would send messengers to each house, asking the householders to bring a child closest to one year of age – if there were no child of one year, to bring the youngest child over 6 months of age.

In April 2008, following the introduction of a monthly weighing of children under three years in a growth monitoring programme, very accurate registers of children and their ages were available. Collections in this batch were made by visiting each household in person. From the list, the names of children from that household of the right age for the

study were read, and the householder would bring the child most easily available. At the same time taking the nasopharyngeal sample and recording the longitude and latitude of the house taken from a global positioning satellite receiver. This was done to enable the location of all households to be plotted, along with the sensitivities of *Streptococcus pneumoniae* isolated. From this data, any clustering of resistance could be discerned, looking especially for clustering of resistance in households close to the health worker's house.

Consent

Consent to collect a nasopharyngeal sample from a child was sought from parents or heads of household. Issues surrounding consent are discussed in section 3.4.1 below.

Sample collection and initial plating out.

After obtaining consent, a nasopharyngeal sample was taken using a dacron swab on a thin wire (Medical Wire & Equipment, Corsham, Bath, UK), as shown in Image 2.20.

Image 2.20 Taking a nasopharyngeal swab with a dacron wire.

In the batches taken 2006-7, the sample was plated directly onto a sheep blood crystal violet agar plate (sheep blood agar base, Oxoid, with 5% sheep blood and 1:50 000 crystal violet, (Garrod 1942)), with two samples per plate. These were taken from and then replaced into a cylindrical metal container, which was then placed in a polystyrene box with hot water bottles in it. This was done because the outside temperature in the winter is very cold – down to minus 25° Centigrade at night and below freezing at midday. The temperature inside the box was monitored with a maximum/minimum thermometer, and it was usually between 20° and 27° Centigrade. On finishing the collection for the day, the samples were taken back to the lab in Kipkut, and optichin discs applied to the plates before they were put in the candle jar (see below) and into the incubator.

Using such a system led to relatively high contamination rates. Since whenever a collection was made we were honoured guests, the host would light a fire in the stove in the room in which we sat. Inevitably, the room would fill with smoke, and particulates would land on the plates, no matter how quickly they were opened and closed. The rooms were also very dusty, and with large numbers of people coming and going in a very small space, there was a lot of dust in the air.

In the collection made in 2008, nasopharyngeal swabs were inserted into 2ml slopes of Dorset Egg medium prepared in a swab tube from which the swab had been removed, but the stopper retained - the swab wire was cut with sterile scissors. To take the sample, the sample swab's seal was broken and the swab removed from the tube. After taking the swab, the swab was placed in the Dorset egg tube, and that tube's stopper discarded. As well as reducing environmental contamination of the sample, this system meant that a much smaller volume of equipment needed to be carried, especially as the collection was being done house to house to collect GPS mapping data. The swabs were kept warm in the bag with a hot water bottle filled with water at around 40° Centigrade and wrapped in a blanket. Once the collection was completed, the samples were taken to the laboratory and plated out. An optichin disc (Oxoid Ltd) was applied to each sample.

2.4.2 Initial incubation

The plates were placed in candle jars and incubated at 37° Centigrade overnight. The candle jars were modified pressure cookers. These were cheap and widely available. The valves on the lid were removed, the holes sealed with rubber washers and bolts, and the gasket coated in vaseline. A five litre pressure cooker held 24 plates, and fitted

well inside the incubator. Four white 'tea-light' candles were used to increase the carbon dioxide levels in each candle jar.

2.4.3 Isolation of *Streptococcus pneumoniae*

After overnight incubation, the plates were examined. Opticin sensitive, alpha haemolytic mucoid colonies with a morphology suggesting *Streptococcus pneumoniae* were replated onto crystal violet sheep blood agar. The second plates were not incubated in carbon dioxide.

2.4.4 Identification of *Streptococcus pneumoniae*

Colonies were replated until a pure growth was obtained. *Streptococcus pneumoniae* was identified by growth on crystal violet blood agar, colonial morphology, alpha haemolysis, optichin sensitivity and bile solubility (one drop of sodium deoxycholate 10% solution is dropped on the colony and incubated at 37˚ centigrade for 30 minutes; the test is positive if the colony disappears).

2.4.5 Disc sensitivities

Sensitivity testing was conducted in accordance with the Clinical and Laboratory Standards Institute Performance Standards for Antimicrobial Susceptibility Testing; Fifteenth Informational Supplement (2005). Two or three colonies were suspended in 1ml of sterile deionised water to give a Macfarlane number 1 suspension, which was then spread onto Mueller-Hinton agar (Oxoid Ltd) with 5% sheep blood. Anti-microbial discs for optichin, trimethoprim-sulphamethoxazole, oxacillin, erythromycin and tetracycline were applied using a 6 disc dispenser. The plates were incubated overnight

in carbon dioxide. Two or three colonies from the 'pure growth' plate were also replated onto blood agar in readiness to provide fresh colonies for E-testing if required.

After overnight incubation, zone sizes were measured with a Vernier caliper. Resistance and intermediate susceptibility were recorded if the zone around the disc was less than the CLSI 2005 standard breakpoint diameter:

antibiotic disc	sensitive	intermediate	resistant
oxacillin	≥ 20mm	(N/A)	≤ 20mm
cotrimoxazole	≥ 19mm	16-18mm	≤ 15mm
erythromycin	≥ 21mm	16-20mm	≤ 15mm
tetracycline	≥ 23mm	19-22mm	≤ 18mm

2.4.6 Minimum inhibitory concentration, by E-test

If resistance was recorded, then Macfarlane number 1 suspensions were prepared from the newly incubated plate, and E-strips applied (Bio Disk, France). Only a limited number of E-strips were available, so it was not possible to obtain a minimum inhibitory concentration for every isolate demonstrating resistance. 93 isolates were e-tested for co-trimoxazole (29 in 2006, 63 in 2008), 5 for erythromycin (all in 2008), 14 for penicillin (13 in 2006, and one in 2008), and 43 for tetracycline (16 in 2006, and 27 in 2008).

2.4.7 Quality control

In the 2008 collection, control strains of *Streptococcus pneumoniae* (ATCC 49619) were cultured from *Cultiloops* (Remel, USA) and maintained. Sensitivities of the control strains were carried out every week. In the November 2006 – January 2007 collection, despite repeated attempts the *Cultiloop* strains did not grow. Streaking the plate and

broth incubation methods were both attemped, but neither yielded any growth. However, since the methods and results from the two collections were similar, there is no reason to suggest that the absence of control strains in the first collection invalidates the results.

2.4.8 Variation in winter 2006-7

In November 2006, a consignment of equipment failed to reach Kabul in time to be transported to Kipkut for the winter season. In late November and December, 68 samples were processed in Kipkut, after which supplies of antimicrobial discs and e-strips were exhausted. In January 2007, 124 samples were taken, plated onto sheep blood agar, incubated overnight, and then first growth streaked onto Dorset Egg medium, appropriately packed and transported to Kabul, where they were analysed in the National Central Laboratory seven days later. There was no facility in Kabul to make media, so in anticipation of this, ready prepared sheep blood agar plates (without crystal violet) and Mueller-Hinton with sheep blood plates (both from Oxoid) were imported from the UK. In the Central Laboratory, there was a 5% carbon dioxide atmosphere incubator, so candle jars were not used. Isolation, sensitivities and e-testing was done using the methods described above.

2.4.9 Data analysis

Isolation and inhibition zone sizes around the antibiotic discs were entered into a database (Open Office Base), and arranged by household. Isolation rates were calculated and tabulated by year, age and sex. Resistance rates were calculated using the breakpoints detailed above, and tabulated by age and sex. This data was then

converted into a csv file and analysed as a logistic regression, using STATA statastics software.

In the first analysis, all age bands were compared with the first age band (under 12 months), looking for variation for age in bands, adjusted for year and sex.

```
. xi: blogit pos_carr tot_carr i.age_band i.year sex
i.age_band        _Iage_band_1-7      (naturally coded;
_Iage_band_1 omitted)
i.year            _Iyear_1-3          (naturally coded; _Iyear_1
omitted)
```

In the second analysis, variation by age as a trend (rather than banded categories), using under 12 months as the reference age.

```
. xi: blogit pos_carr tot_carr age_band i.year sex
i.year            _Iyear_1-3          (naturally coded; _Iyear_1
omitted)
```

Ideally this analysis should have been done entering all the individual data, rather than banded data. However, precise age is unknown in each case, so banded date was used.

Analysis were also performed for comparison of isolation rates by sex.

Data for isolation rates by year was analysed with a *chi* squared 2x2 table from http:// statpages.org/ctab2x2.html, comparing each year with the others.

Data from the second year of collection (2006-7), comparing isolation rates in Kipkut and in Kabul, and also comparing isolation rate in the Kipkut laboratory with in 2007-8 with isolation rate in Kipkut in 2008 was analysed with a *chi* squared 2x2 table from http://statpages.org/ctab2x2.html

Resistance and intermediate sensitivity was tabulated for each antibiotic, and rates calculated. A chi squared 2 way contingency calculation using http://statpages.org/ctab2x2 was performed, comparing rate of resistance to each antibiotic in 2006-7, with resistance rate to each in 2008 for all ages and both sexes together, and rate of (resistant + intermediate sensitivity) to each antibiotic in 2006-7, with rate of (resistant + intermediate sensitivity) to each in 2008 for all ages and both sexes together.

Multiple resistance was also calculated and tabulated. Paired resistances were also calculated, and p values for the comparison between rates of paired resistances in 2006-7 and 2008 were calculated using *chi*-squared test in 2x2 tables, at http://statpages.org/ctab2x2.html

2.4.10 Transportation of isolates to UK

In April 2008, isolates demonstrating resistance were stored on blood agar plates for further analysis. Unfortunately, the supply of plates was cut when the man who looked after the sheep which provided blood for the agar plates forgot to come to the laboratory one morning and sent the sheep up the mountain to graze. This meant that more than half the isolates were lost. 16 were salvaged, and put onto Dorset egg slopes in 5ml bijou bottles. These were packed in an appropriate secure container and hand-carried overland to Dushanbe, the capital of Tajikistan. In Dushanbe, the box was transferred to a WHO-approved transportation container sent from the UK. To prevent the samples from becoming too cold in the hold of the aircraft, the sample box was wrapped in a blanket, and then put into transportation box with a hot water bottle at around 50° Centigrade wrapped in a blanket. The isolates were sent to the Wellcome Sanger Institute Genome Campus in Hinxton, Cambridge, where they were put into a refrigerator in error. From there, the isolates were sent to the laboratory of University of Liverpool Division of Medical Microbiology & Genito-urinary Medicine. Here they were

plated out by the laboratory staff, grown and then frozen at -70° Centigrade on latex beads. 12 of these 16 isolates survived, and were used for quality control.

2.4.11 Confirmation of Wakhan results on UK isolates

Unfortunately, it was not possible to do the planned analysis in Liverpool, so the isolates were unfrozen and plated out and sent to St George's Hospital in Tooting, London. Here, the isolates were plated out by the laboratory staff, and the next day, the author re-plated them and reconfirmed their identity, again using optichin sensitivity, alpha haemolysis, colonial morphology and bile solubility. In addition to these tests, a latex agglutination test *(Pneumoslide,* BD Diagnostic Systems, Maryland USA) was also used to confirm the identity as *Streptococcus pneumoniae).* Inhibition zone sizes around antibiotic discs were also repeated.

2.4.12 Serotyping and molecular studies

The isolates were then placed on chocolate agar slopes and sent to the Health Protection Agency (HPA) Centre for Infections at Colindale. Here the isolates were serotyped by the author, using two methods. First, they were analysed on the automated system using the Bio-Plex assay on the Caris instrument (Bio-Rad Laboratories, USA). This system is used at the HPA to identify 14 common serotypes in large batches. All isolates were also typed by the latex agglutination technique, using sera from Statens Serum Institut, Copenhagen, Denmark.

After typing, the isolates were given to the Centre for Infections, and multi-locus DNA sequence typing was requested. Health Protection Agency staff did multi-locus sequence typing according to the standard procedures, and the results were communicated to the author.

2.4.13 GPS plotting

The position (latitude and longitude) of each household was plotted by Dr Chris Lane at Health Protection Agency, Colindale using MapInfo Professional v9.0 software. Information on isolation and resistance of *Streptococcus pneumoniae* to co-trimoxazole and tetracycline, from children in each household in 2008 was indicated. Oxacillin susceptibility was not plotted, as only five isolates were resistance. These charts were then examined by Dr Lane to discern any clustering of resistance. No formal mathematical modelling was used for this.

3 Results

3.1 The population and its health, before the medical programme started

The survey of 2002 confirmed the findings of the initial reconnaissance of 2000, that there was no health service provision and no regular work by any NGO in the upper part of Wakhan District in 2002.

3.1.1 Population and demography, 2002

25 communities betweeen Qala-e-Panja and Sarhad-e-Boroghil were surveyed, comprising a total of 513 households. These are shown on Map 2.1 on page 45 above. Of these, 171 should have been surveyed. One was excluded due to a bereavement and two were excluded as being too inaccessible, thus 168 households were surveyed representing 32.74% of the total. These three houses were visited subsequently in the course of the health programme, and there is no reason to believe that the exclusion of these households from the data collection in 2002 made a significant difference to the results of the survey.

These 168 households had a population of 1863 people, 987 (53%) males and 876 (47%) females. 782 (42%) of these were under 15 years old, and 19% were under five years. The estimated population is thus 5690. The average household size was 11.1 people.

The Charts 3.1 and 3.2 show the age distribution of males and females.

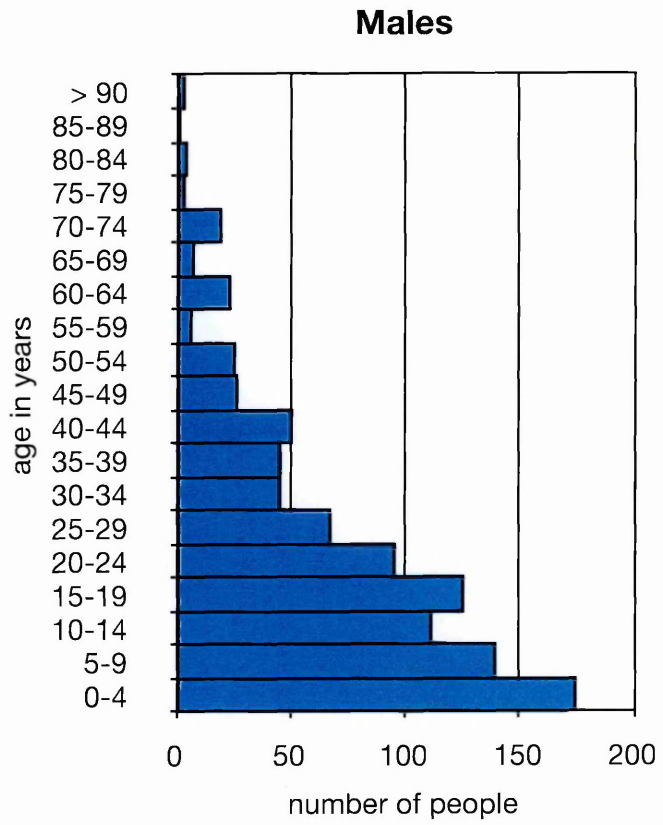


Chart 3.1 Numbers of males by age band in 2002

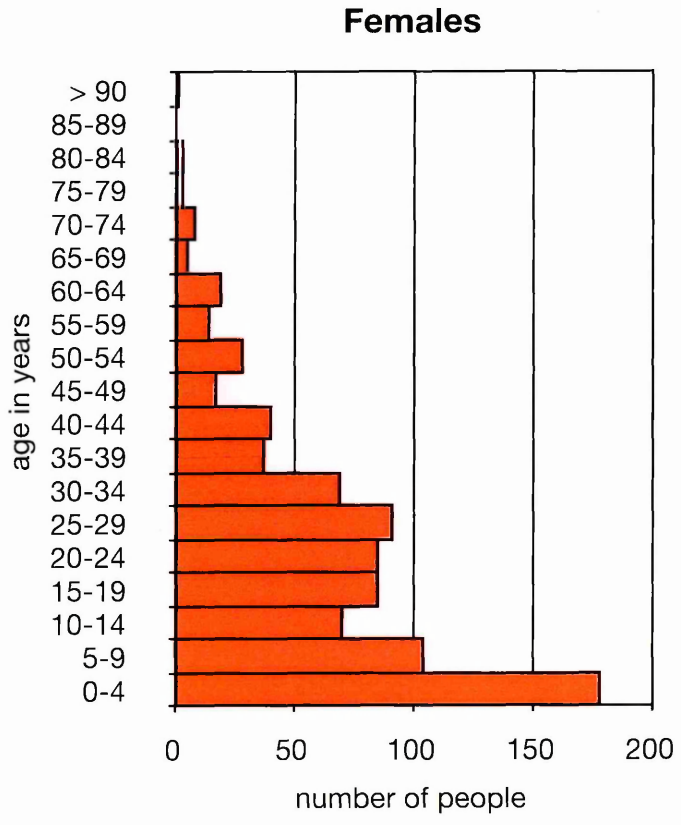


Chart 3.2 Numbers of females by age band in 2002

Chart 3.3 compares the distribution of males and females by age, as a percentage of the total population.

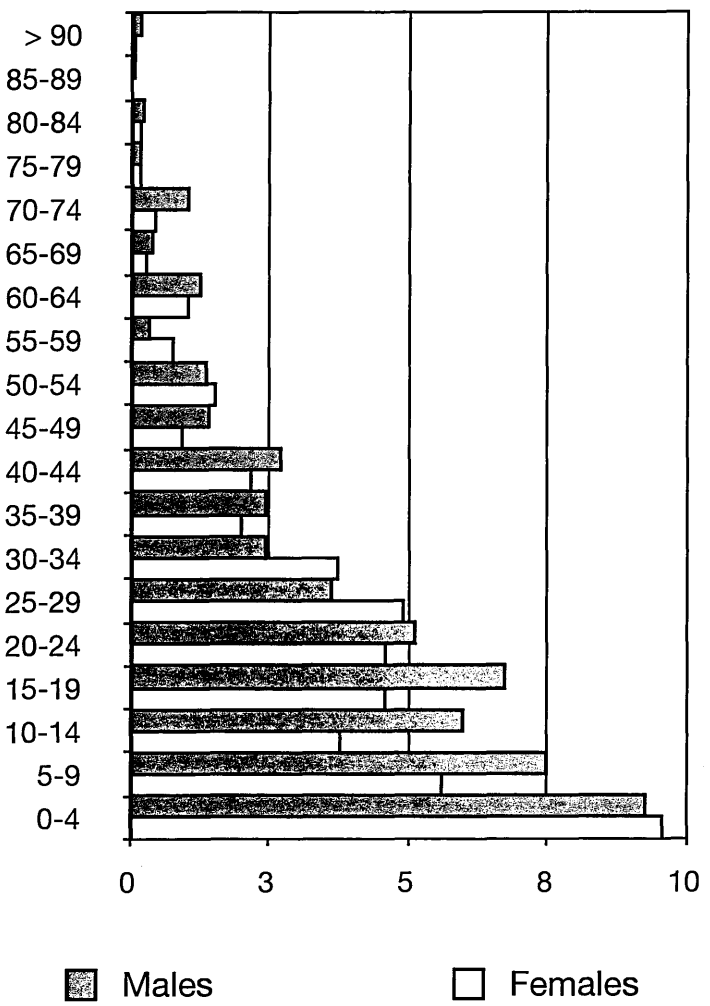


Chart 3.3 Males and females in each age group as a percentage of the total population

In the age group 5-24 years, there is a significantly greater number of males ($p=<0.0001$).

3.1.2 Health data from survey of 2002

3.1.2.1 Neonatal, infant and child mortality

647 births and 190 deaths were reported in children under 59 months of age in the period 1995-2002.

Table 3.1 shows figures for reported births, and deaths among children under 59 months in period 1996-2002.

year of birth	alive	died 0-1m	died 1-11m	died 12-23m	died 24-59m	died >59m	total deaths	births
1996	42	5	6	4	8	3	26	68
1997	68	11	7	1	8	2	29	97
1998	58	12	10	8	2		32	90
1999	77	18	8	5	0		31	108
2000	74	14	12	4	5		35	109
2001	91	10	5	3			18	109
2002	52	6	8				14	66
	462	76	56	25	23	5	**185**	**647**

*Some of these deaths may be stillbirths rather than neonatal deaths.

Table 3.1 Births and deaths among children in Wakhan under 59 months.

There were five deaths in children born before 1996, but died during the period, 1996-2002.

Mortality rates were calculated by two methods. The first assumed a steady state, that birth and death rates remained constant during this period. Rates were calculated by ((deaths ÷ births)x1000). Rates are shown in Table 3.2.

Mortality rate under 28 days (per 1000 live births)	120
Mortality rate under 12 months (per 1000 live births)	211
Mortality rate under 59 months (per 1000 live births)	292

Table 3.2 - mortality rates for different age groups, assuming a 'steady state'.

For purposes of comparison with data collected after 2004, rates were also calculated for cohorts born in each year, following through each to 24 months of age. Rates for 12-23 months could not be calculated for those born in 2000 and 2001, and rates for 0-11m could not be calculated for those born in 2001 and 2002 as the full period had not elapsed for all children by August 2002. Table 3.3 shows rates for each cohort, and an aggregate rate.

year of birth	rate 0-1m	rate 0-11m	rate 0-23m
1996	74	162	221
1997	113	186	196
1998	133	244	333
1999	167	241	287
2000	128	239	
2001	92		
2002	91		
aggregate rate	**117**	**218**	**262**

all rates are per 1000 live births

Table 3.3. mortality rates for annual cohorts followed from 24 months from birth, 1996-2002

Mortality rates for data subsequently collected during the establishment of the project are given in section 3.2.2, and a comparison is made and discussed.

3.1.2.2 Causes of death among children

Table 3.4 shows reported causes of death for 180 children under 59 months who were reported to have died in the birth cohorts preceding 2002, which were analysed.

Cause	0-1m	1-11m	12-23m	24-35m	36-59m	total
acute respiratory infection	4	15	10	6	1	36
diarrhoea		1	1	3		5
other abdominal cause		11	3	2		16
measles	1	5	1	2	1	10
cause unknown (less than 28d)	71					71
cause unknown (more than 28d)		12	5	1		18
other infection		10	3	4	1	18
Shigella diarrhoea		1	2	1	1	5
trauma					1	1
	76	55	25	19	5	180

* Some of these may have been still births, rather than neonatal deaths.
**All deaths from bloody diarrhoea occurred in a confirmed Shigella epidemic in the winter of 2001-2002.

Table 3.4 Reported causes of death in 2002 in children in Wakhan under 59 months

Table 3.5 shows reported causes of death for 180 children under 59 months, by percentage

Cause	0-1m	1-11m	12-23m	24-35m	36-59m	total
	%	%	%	%	%	
acute respiratory infection	*5*	*27*	*40*	*32*	*20*	*20*
diarrhoea		*2*	*4*	*16*		*3*
other abdominal cause		*20*	*12*	*11*		*9*
measles	*1*	*9*	*4*	*11*	*20*	*6*
cause unknown (less than 28d)	*93*					*39*
cause unknown (more than 28d)		*22*	*20*	*5*	*0*	*10*
other infection		*18*	*12*	*21*	*20*	*10*
Shigella diarrhoea		*2*	*8*	*5*	*20*	*3*
trauma						*1*
						100

Table 3.5 Reported causes of death in 2002 in children in Wakhan under 59 months, by percentage

In only 51% of cases can a firm cause of death be given (respiratory illness, measles, bloody diarrhoea, diarrhoea and trauma). All the other causes of death reported were vague, and an attempt was made to categorise them in the table above.

There is a specific word for 'measles' in both Dari and Wakhi languages. The disease has a very characteristic pattern of a prodromal illness, followed by a rash spreading from the head down the body. Before the survey started, a discussion was had with Turob, the local surveying assistant, concerning how the word was used, and the author was confident that it was only used to describe measles. Another word was used to describe a rash that would be called 'chicken pox' in the UK. In contrast to these, the word used by Afghan doctors for whooping cough (*sya sulfa,* meaning literally 'black cough', presumably from the dark colour of the lips at the end of a coughing bout) was used very loosely in Wakhan to describe any serious cough. The data recorded on the survey form (in Appendix 1) concerning the specific question on whooping cough was therefore not used, and any deaths attributed to *sya sulfa* were recorded as deaths from acute respiratory infection.

Cause of death among children in the period 2004-8 are recorded in section 3.2.3.

3.1.2.3 Nutritional status

Table 3.6 shows rates of malnutrition by measurement of mid upper arm circumference (MUAC) measurements by age.

	12 - 23 m		24 - 35m		36 - 47m		48 - 59m	
	number	%	number	%	number	%	number	%
Measured	68		45		52		43	
>12.5cm	34	*50*	35	*78*	44	*85*	37	*86*
11-12.4cm	25	*37*	10	*22*	8	*15*	6	*14*
<11cm	9	*13*	0	*0*	0	*0*	0	*0*

MUAC of above 12.5cm indicates normal nutrition, between 11 and 12.4 cm moderately underweight, and below 11cm, severely underweight.

Table 3.6 MUAC by age in Wakhan children in 2002

The figures in Table 3.4 demonstrate that malnutrition is a significant issue in the population surveyed. It may contribute to the observed and estimated high child mortality.

The survey also asked householders the age at which children in that household generally received their first solid food, as late complementary feeding may contribute to malnutrition.

Table 3.7 and Chart 3.4 show the range of ages at which households reported first giving solid food to children in that household.

age	number of households*	%
6-9 m	7	*5*
10-15 m	65	*42*
16 - 21m	40	*26*
22 - 27m	27	*18*
28 - 48m	15	*10*
total	154	

*14 households did not give an answer.

Table 3.7 Age of first solid food reported in 2002, by number of households surveyed.

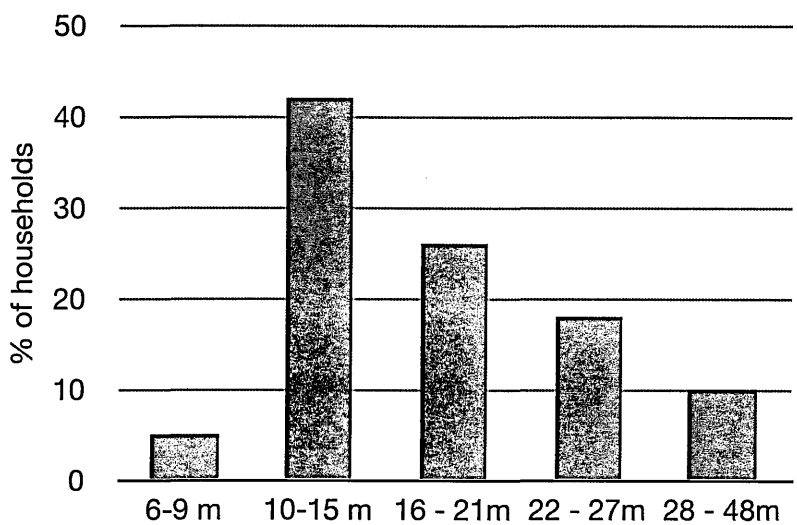


Chart 3.4 Age of first solid food reported in 2002 as a percentage of all households surveyed

More than half the children were reported as not being given solid food before 16 months. The WHO recommendation is to start solid food as 'complementary to breast milk' at six months of age. The delay in introduction of solid food probably contributes to high rates of malnutrition in the second year of life shown in Table 3.4.

3.1.2.5 Vaccination coverage

Recording vaccination coverage gives an indication of access to certain health services that a community enjoys, and can also 'hint' at the causes of death of children in a community. For example, low tetanus coverage can suggest that some deaths in the early neonatal period may be caused by tetanus, as maternal vaccination before delivery protects children from tetanus infection after delivery by ante-natal transplacental antibody transfer.

Table 3.8 shows coverage of childhood vaccination for the six standard vaccines in the first year of the UNICEF Expanded Programme of Immunization (BCG at birth, diphtheria, tetanus and pertussis (DTP) combined vaccine, with oral polio, three doses at two, three and four months of age , measles vaccine at nine months).

	DTP*		**Polio**		**BCG**		**Measles**	
Age range eligible	6 - 59m		6 - 59m		6 - 59m		9 - 59m	
No in age range	344		344		354		305	
		%		*%*		*%*		*%*
1 dose	24	*7*	24	*7*	117	*33*	98	*32*
2 doses	33	*10*	43	*13*				
3 doses	57	*17*	49	*14*				
Recalled vaccination, but no card	4	*1*	139	*43*			119	*39*
Unrecorded			2	*1*				
Not vaccinated	**226**	***66***	**87**	***25***	**237**	***67***	**88**	***29***

*Diphtheria, tetanus and pertussis

Table 3.8 Reported vaccination coverage among Wakhan children under five years in 2002

Table 3.9 shows coverage of tetanus toxoid vaccination in women between 15 and 45 years of age.

Number eligible	413	%
Not vaccinated	204	*49*
1 dose	13	*3*
2 doses	104	*25*
3 doses	74	*18*
Women who recalled vaccination, but had no card	18	*4*

Table 3.9 Tetanus toxoid vaccination coverage for women aged between 15 and 45

Half the women of child bearing age are unvaccinated, and only 18% have received 3 doses. This may have an effect on early neonatal mortality from tetanus.

All of these vaccinations had been administered by mobile teams from the Ministry of Public Health travelling into Wakhan on a sporadically, aided occasionally by staff from FOCUS, a relief organisation in the Aga Khan Development Network. The only consistent programme was the national campaign for polio eradication, which ran relatively well organised national immunisation days. Polio is an oral vaccine, and lay people, such as school teachers, can be trained to administer it, so coverage tends to much better than other vaccines requiring injection everywhere where such campaigns are run.

Figures for both children and women of childbearing age show that vaccination coverage in Wakhan is very poor, and any programme of health intervention needs to address this situation.

The survey form (Appendix 1) also asked for information about addictions, which could effect child care and thus child mortality. 13% of adults were reported to have used opium in the past, but to have stopped. No-one in the households surveyed admitted current use, but told the team of other users in other other households. There is great shame associated with opium use, so under-reporting is inevitable. ORA International, the organisation for which the author was working, had run an opium rehabilitation programme in the area two years previously, and it is unlikely that anyone would confess to having relapsed.

Questions about access to medical services and medicines all received the same answer. When people are ill, they stay at home, as the nearest clinic is more than a day's journey away by donkey. The only medicines available are sold by travelling traders, and the supply of these is very intermittent. It was also clear that people did not know how to use the medicines they bought.

3.1.3 Discussion

3.1.3.1 Reliability of the 2002 survey results

Are the selected households representative?

The team worked hard to ensure that the households surveyed were selected at random. On many occasions, Turob, the local man helping with the survey would suggest that a certain household 'would be a good household to survey'. This suggestion was always resisted and only the households selected by the drawing of numbers from the hat were surveyed.

Are the figures for child death reliable?

The figures recorded for the number of deaths among very young children may be low, especially in the earlier cohorts. Men, in general, did not accurately recall the deaths of

children under two years of age. This became clear when women were questioned about maternal mortality, and child deaths were reconfirmed. The women present remembered their own children, and more recent deaths among the children of absent women from the same household, but seemed not to remember deaths that occurred in young children other than their own more than four or five years before. Thus the figures for the 1996-97 cohort are probably low, and the figures from the other two cohorts may be more representative.

Issues surrounding vaccination

In Table 3.6, the category 'Women who recalled vaccination, but had no card' was added because after some vaccination rounds, the NGO helping the government vaccinators collected the vaccination cards once the course was completed. The figure for measles in this category is probably reliable, as measles is a well-recognized problem in the valley, and the vaccination is a single injection. Figures for polio are probably less reliable as recall as to how many of the three rounds were received is likely to be less accurate.

Low coverage for tetanus toxoid vaccination for women of child-bearing age may be affected by the practice of transhumance. A significant number of women go to the high pastures with the animals in the summer; they may have been absent when the vaccination team came. However, there were other women who were present in the village when the vaccinators came who still did not present for vaccination.

3.1.3.2 Possible causes of high mortality in children under five years

The survey data revealed a perception within the community of poor food security, and showed hard data on poor access to health care facilities, high levels of malnutrition among young children and very high levels of child mortality and maternal mortality.

The international literature shows that malnutrition, indoor smoke pollution, overcrowding, and lack of access to health services are all associated with increased child mortality (section 1.2.2). The results of the survey clearly demonstrated that these conditions are present in the area examined.

As also expected from the international literature, acute respiratory illness was found to be an important cause of death in children under five years of age. Malnutrition, indoor smoke pollution and overcrowding are risk factors for acute respiratory illness, and high altitude, and associated reduced oxygen tension may increase mortality in acute respiratory illness.

3.1.3.3 Need to intervene at as many points as possible

In designing the health programme to reduce child mortality, it was necessary to incorporate appropriate and easily implemented interventions to reduce the effect of as many contributing factors as possible. Some issues, such as high altitude and poor weather, cannot be altered. However, many other factors can be addressed, with a 'three-pronged' approach:

1. Provision of simple curative and preventative medical services, such as treatment of common illness, especially acute respiratory infection in children, vaccination and micronutrient supplementation.

2. A community health education programme to work on prevention of ill health through better nutrition and feeding practice, more proactive 'illness behaviour', and lifestyle changes promoting better health.
3. 'Non-medical' interventions to improve health, such as action to tackle food security and reduce indoor smoke pollution.

The programme set up by ORA International adopted this three-pronged approach.

3.2 Results of continual data collection, 2004 - 2008, after the establishment of the project

3.2.1 Child mortality data

Data were regularly collected from November 2004 to April 2008, by asking the female community health workers in each village, who had been trained in the programme, about births and outcomes, and about deaths and causes of death. This information was recorded in a register.

In this period, a total of 772 births were reported, of which 12 were reported as stillbirths. Whether the children were born alive is impossible to verify, so these are included as neonatal deaths.

A total of 141 deaths were reported in children under 59 months, of which 54 (38%) were in children under 28 days, 47 (40%) were in children from 1-11 months, 26 (18%) were in children 12 - 23 months and 4 (3%) in children 24- 59 months.

Children born in the period were included in three cohorts for the calculation of mortality rates. Only those who had reached the cut off age in the birth cohort were included in this analysis. These are shown in table 3.10

birth period	births	death 0-1m	death 1-11m	death 12-23m	total
11.04-05.06	380	19	27	14	60
6.06-5.07	261	24	21	4	49
6.07-5.08	131	11	9	0	20
total	772	54	57	18	129

Table 3.10 births and deaths from 11.2004- 5.2008

As the period of follow-up was less than five years, it is not possible to calculate mortality figures for 0-59m. Figures were thus calculated for completed cohorts.

772 children were born in the period 11.2004 - 4.2008, and thus had the potential to reach 28 days of age by the end May 2008. 54 children died before reaching 28 days. **This gives a mortality rate for under 28 days of 70 deaths per 1000 births.**

641 children were born in the period 11.2004 - 4.2007, and thus had the potential to reach one year of age by the end May 2008. 91 died before reaching 12 months of age. **This gives a mortality rate for under one year of 159 deaths per 1000 births**

380 children were born in the period 11.2004 - 5.2006, and thus had the potential to reach two years of age by the end May 2008. 60 died before reaching two years of age. **This gives a mortality rate for under two years of 158 deaths per 1000 births.**

3.2.2 Comparison with mortality before the project began

Table 3.8 compares mortality rates in birth cohorts before and after the start of the health programme, and shows that mortality rates are significantly reduced in all age groups.

	0-1m	0-11m	0-23m
births in cohort 1996-2002	647	472	463
died	76	103	95
rate per 1000 births	**117**	**218**	**262**
births in cohort 11.2004-5.2008	772	641	380
died	54	91	60
rate per 1000 births	**70**	**159**	**158**
p value	0.002	0.001	0.000

Table 3.11 Comparison of mortality rates for periods 1996-2002 and 2004-2008

These data show a significant reduction in mortality in children under in all three age groups.

3.2.3 Causes of death

Table 3.12 overleaf shows that acute respiratory illness was the most common identified cause of death in children under two in the period 2004-2008, the results shown three cohorts.

There was no significant difference between rates of death from any one cause in the two time periods. The large proportion of deaths from unknown causes in the period 2004-8, especially in children over one month of age, contributed to this.

Cause of death	0-1m	1-11m	12-23m	total	births
Cohort 1 11.2004-5.2006					380
acute respiratory infection	1	6	6	**13**	
diarrhoea			1	**1**	
cause unknown (less than 28d)	17			**17**	
cause unknown (more than 28d)		8	4	**12**	
other infection		1	1	**2**	
other abdominal cause				**0**	
measles	1	12	2	**15**	
total	**19**	**27**	**14**	**60**	
Cohort 2 6.2006-5.2007					641
acute respiratory infection		8		**8**	
diarrhoea				**0**	
cause unknown (less than 28d)	23			**23**	
cause unknown (more than 28d)		8	1	**9**	
other infection		3	2	**5**	
other abdominal cause	1	2	1	**4**	
measles				**0**	
total	**24**	**21**	**4**	**49**	
Cohort 3 6.2007-5.2008					772
acute respiratory infection		2		**2**	
diarrhoea		1		**1**	
cause unknown (less than 28d)	11				
cause unknown (more than 28d)		6		**6**	
other infection					
other abdominal cause					
measles					
total	**11**	**9**	**0**	**20**	
Combined					
acute respiratory infection	1	16	6	**23**	
diarrhoea	0	1	1	**2**	
cause unknown (less than 28d)	51			**51**	
cause unknown (more than 28d)		22	5	**27**	
other infection	0	4	3	**7**	
other abdominal cause	1	2	1	**4**	
measles	1	12	2	**15**	
total	**54**	**57**	**18**	**129**	

* Some of these may have been still births, rather than neonatal deaths

Table 3.12 Causes of death in children under two years in the period 2004-2008 in Wakhan

Table 3.13 shows causes of death in children under two years in the period 2004-2008 in Wakhan, by percentage of total deaths

Cause of death	0-1m	1-11m	12-23m	total
Cohort 1 11.2004-5.2006	%	%	%	%
acute respiratory infection	5	22	43	22
diarrhoea			7	2
cause unknown (less than 28d)	89			28
cause unknown (more than 28d)		30	29	20
other infection		4	7	3
other abdominal cause				
measles	5	44	14	25
total				100
Cohort 2 6.2006-5.2007				
acute respiratory infection		38		16
diarrhoea				
cause unknown (less than 28d)	96			47
cause unknown (more than 28d)		38	25	18
other infection		14	50	10
other abdominal cause	4	10	25	8
measles				
total				100
Cohort 3 6.2007-5.2008				
acute respiratory infection		22		10
diarrhoea		11		5
cause unknown (less than 28d)	100			55
cause unknown (more than 28d)		67		30
other infection				
other abdominal cause				
measles				
total				100
Combined				
acute respiratory infection	2	28	33	**18**
diarrhoea		2	6	**2**
cause unknown (less than 28d)	94			**40**
cause unknown (more than 28d)		39	28	**21**
other infection		7	17	**5**
other abdominal cause	2	4	6	**3**
measles	2	21	11	**12**
total				100

Table 3.13 Causes of death as a percentage of the total deaths in children under two years of age.

3.2.4 Growth monitoring data

A total of 2623 measurements were taken on 907 children up to 30 months of age between April 2007 and May 2008.

Using the World Health Organization growth monitoring charts, z scores for deviation from the mean were calculated. Charts 3.5 and 3.6 show the distribution of z scores for boys and girls surveyed in this period.

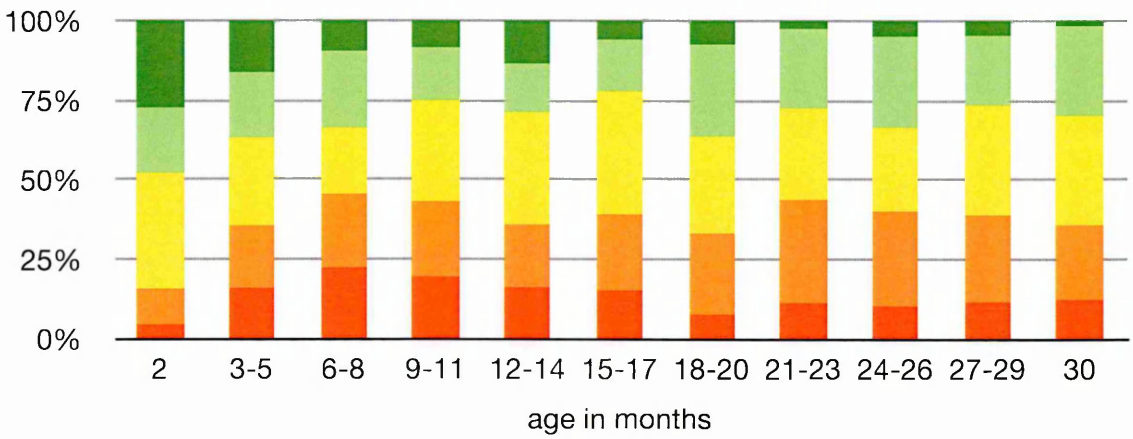


Chart 3.5 Percentage of boys aged 2-30 months in z score bands, April 2007-May 2008.

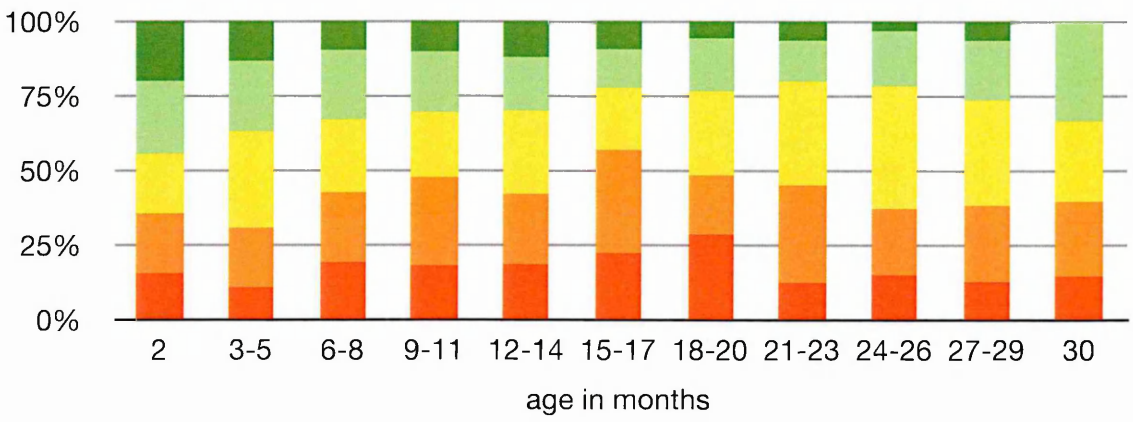


Chart 3.6 Percentage of girls aged 2-30 months in z score bands, April 2007-May 2008.

- Weight with z score above mean
- Weight with z score between mean and -1
- Weight with z score between -1 and -2 from mean
- Underweight (z score between -2 and -3 from mean)
- Severely underweight (z score below -3 from mean)

Table 3.12 shows the number of children in z score bands.

age (m)	z score	male		female		
		no.	%	no.	%	p value
2 - 11						
	>-2	158	*43*	210	*44*	
	<-2 but >-3	78	*21*	115	*24*	
	< -3	66	*18*	77	*16*	0.517
	total < -2	144	*39*	192	*40*	0.776
total		368		479		
12 - 23	>-2	277	*49*	167	*32*	
	<-2 but >-3	142	*25*	146	*28*	
	< -3	73	*13*	105	*20*	0.001
	total < -2	215	*38*	251	*48*	0.001
total		565		523		
24 - 30	>-2	180	*50*	163	*50*	
	<-2 but >-3	100	*28*	85	*26*	
	< -3	40	*11*	40	*12*	0.248
	total < -2	140	*39*	125	*38*	0.834
total		360		328		

Table 3.14 Number and percentage of children in z score bands, April 2007 - May 2008

p values were calculated using the Pearson chi-squared test in 2x2 tables, without Yates' continuity correction (at http://statpages.org/ctab2x2.html)

Chart 3.7 shows a comparison between boys and girls in low weight-for-age z score bands.

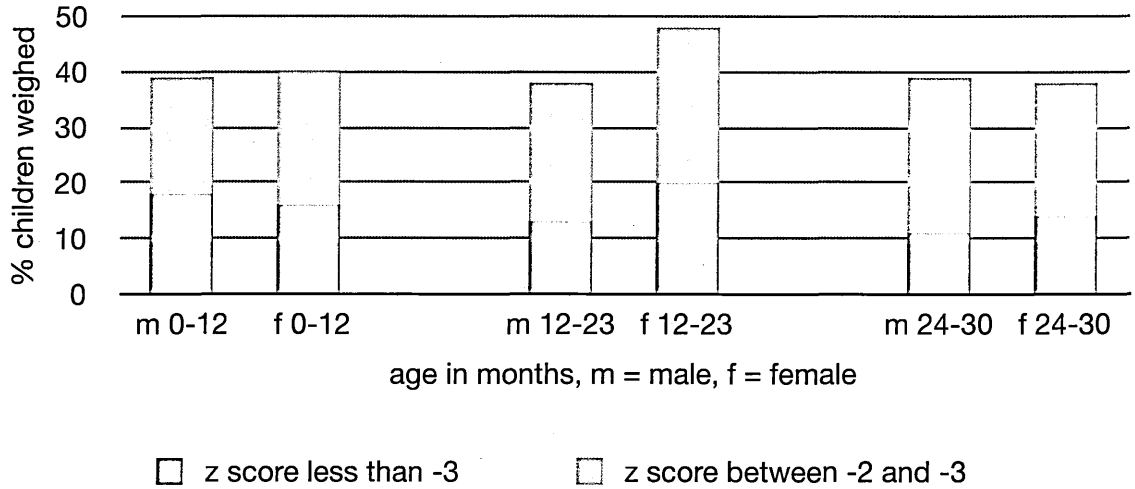


Chart 3.7 Comparison of boys and girls in low weight for age z score bands, April 2007-May 2008.

It is not possible to compare these results with the results for nutritional status data from 2002 (shown in Table 3.1), since a different method for measurement was used.

In the data collected from April 2007-May 2008, there is significantly higher proportion of moderately and severely underweight girls aged from 12 - 23 months compared with boys of the same age. Given the cultural status of girls, it is possible that girls receive less attention, and thus less food at mealtimes, and may also receive fewer snacks between meals.

3.2.5 Discussion

3.2.5.1 Issues surrounding the calculations of child mortality

There was a significant reduction in all mortality rates at the 5% level in the data collected after the implementation of the programme. This represents around 50 lives saved in the period November 2004 - May 2008.

3.2.5.2 Issues surrounding causes of death

Table 3.13 gives reported causes of death for children under five in the period 2005-8 compared with 1996-2002.

'Abdominal pain' is an interesting category. During the survey, it was very common for people to report that the child died after their abdomen swelled up. These were reported as 'abdominal pain' in the survey report. In subsequent data collection, when more time was spent ascertaining what actually happened, it was often reported that the swelling of the abdomen occurred just before death, but that some other disease process was going on before that; this other process was recorded as the cause of death.

The measles deaths occurred before April 2007, when ORA got permission to implement the Government vaccination programme in the project area.

3.2.5.3 Cause of falling mortality

No single known cause of death shows a significant reduction between the two time periods, but there is a significant reduction in overall mortality. This means that it is probable that the interventions in the ORA Wakhan programme had some effect, and that the 'Wakhan *sina baghal* protocol" taught to the village health workers may have been effective, although in this study, it is not possible to rule out confounding factors.

3.2.5.4 Comparative influence of non-pharmaceutical interventions and antibiotic use

In a multiple intervention programme, it is not possible to distinguish the differential effects of pharmaceutical and non-pharmaceutical interventions.

3.2.5.5 Is treatment failure due to emergence of resistance?

Despite the reduction in deaths from acute respiratory infections, 23 children were still reported to have died from ARI (18% of all deaths). It was reported by the health workers in the villages that most of these children received co-trimoxazole. Failure of such treatment to prevent death could be due to several factors:

1. The pneumonia was caused by a virus, which would not be susceptible to co-trimoxazole
2. The treatment was given too late, so that even if the disease-causing organism was susceptible to co-trimoxazole, the antibiotic would not kill it fast enough to prevent death
3. Death was caused by another factor, such as circulatory failure due to dehydration
4. The co-trimoxazole tablets given were ineffective owing to degradation of the drug caused by poor storage
5. An incorrect dose of co-trimoxazole was given
6. The bacterium causing the disease was not susceptible to co-trimoxazole

3.2.5.6 Need for monitoring antibiotic resistance

It is known that use of antibiotics promotes resistance to antibiotics. The Wakhan health programme issued antibiotic supplies to health workers with 20 days' training to distribute according to the adapted IMCI protocol. Such a short period of training may lead to over-use of antibiotics, which in turn could promote resistance and lead to co-trimoxazole becoming ineffective in an unacceptably high proportion of cases.

Given this possible outcome, monitoring levels of resistance to co-trimoxazole in organisms likely to cause disease was appropriate. *Streptococus pneumoniae* and *Haemophilus influenzae* are known to be the most common organisms causing ARI in young children. *Haemophilus influenzae* is a very fastidious organism, and it was judged that surveillance of antibiotic susceptibility of *Haemophilus influenzae* would be too difficult in such a remote location. After extensive consultation over a year with colleagues working with *Streptococcus pneumoniae* in the UK and Malawi, it was decided that surveillance of antibiotic susceptibility of *Streptococcus pneumoniae* was feasible and desirable.

3.3 Surveillance of *Streptococcus pneumoniae*

Section 3.2.3.6 above showed that surveillance of the antibiotic susceptibility of *Streptococcus pneumoniae* was desirable in the area covered by the ORA health project in Wakhan. Having built the laboratory, and established water and power supplies, and supply and communication systems, collection of nasopharyngeal samples commenced in November 2006.

3.3.1 Isolation rates

Table 3.15 overleaf shows the overall isolation rate of *Streptococcus pneumoniae* from nasopharyngeal samples taken from healthy children in three collection periods, by age and sex.

Logistic regression analyses were performed, entering age, sex and year of collection as variables, as described in section 2.4.9 above

There was no significant difference between isolation rates from males and females ($p=0.602$).

There was no significant difference in isolation rate for any age band when compared with age band 0-11 months (p varying from 0.211 to 0.997)

When analysed for 'age as trend' (i.e. rather than comparing individual age bands with the age 0-11 months, this analysis looked for an influence of increasing age on isolation rates), there was also no significant effect (p=0.788).

There was a significant difference in isolation rates by year, using a *chi* suared 2x2 table

2005-6 vs 2008	p = <0.0001
2006-7 vs 2008	p = 0.001
2005-6 vs 2006-7	p = 0.001

	Females			Males			Total		
age range (m)	samples	no. isolated	%	samples	no. isolated	%	samples	no. isolated	%
2005 - 6									
0-11	4	0	*0*	3	0	*0*	7	0	*0*
12-23	10	1	*10*	9	3	*33*	19	4	*21*
24-35	7	0	*0*	6	1	*17*	13	1	*8*
36-47									
48-59									
60-71									
Over 72									
total	**21**	**1**	***5***	**18**	**4**	***22***	**39**	**5**	***13***
2006 - 7									
0-11	13	5	*38*	17	7	*41*	30	12	*40*
12-23	28	14	*50*	23	9	*39*	51	23	*45*
24-35	22	8	*36*	28	14	*50*	50	22	*44*
36-47	19	9	*47*	20	6	*30*	39	15	*38*
48-59	16	4	*25*	1	0	*0*	17	4	*24*
60-71	1	0	*0*	0	0	*0*	1	0	*0*
Over 72	0	0	*0*	2	1	*50*	2	1	*50*
total	**99**	**40**	***40***	**91**	**37**	***41***	**190**	**77**	***41***
2008									
0-11	21	11	*52*	15	7	*47*	36	18	*50*
12-23	43	24	*56*	29	16	*55*	72	40	*56*
24-35	36	20	*56*	33	17	*52*	69	37	*54*
36-47	11	10	*91*	15	9	*60*	26	19	*73*
48-59	7	2	*29*	10	6	*60*	17	8	*47*
60-71	6	3	*50*	1	1	*100*	7	4	*57*
Over 72	5	5	*100*	7	4	*57*	12	9	*75*
total	**129**	**75**	***58***	**110**	**60**	***55***	**239**	**135**	***56***
total 2005-8									
0-11	38	16	*42*	35	14	*40*	73	30	*41*
12-23	81	39	*48*	61	28	*46*	142	67	*47*
24-35	65	28	*43*	67	32	*48*	132	60	*45*
36-47	30	19	*63*	35	15	*43*	65	34	*52*
48-59	23	6	*26*	11	6	*55*	34	12	*35*
60-71	7	3	*43*	1	1	*100*	8	4	*50*
Over 72	5	5	*100*	9	5	*56*	14	10	*71*
total	**249**	**116**	***47***	**219**	**101**	***46***	**468**	**217**	***46***

Table 3.15 Isolation rates of *Streptococcus pneumoniae* from nasopharyngeal samples taken from healthy children in three collection periods, by age and sex.

Table 3.16 shows the isolation rates of *Streptococcus pneumoniae* in samples processed in Kipkut and samples transported to Kabul and processed there in the period November 2006 - January 2007.

age (m)	no. samples taken	no. *Streptococcus pneumoniae* isolated	%
Kipkut			
0-11	15	9	*60*
12-23	22	10	*55*
24-35	16	9	*44*
36-47	9	3	*56*
48-59	4	2	*50*
60-71			
> 72			
total	66	35	*53*
Kabul			
age (m)			
0-11	15	3	*20*
12-23	29	11	*38*
24-35	34	14	*44*
36-47	31	12	*33*
48-59	13	2	*15*
60-71	1	0	*0*
> 72	2	1	*50*
total	124	42	*34*

Table 3.16 Isolation rates of *Streptococcus pneumoniae* in samples processed in Kipkut and in Kabul, 2006-7.

There was a significant difference between isolation rates of samples processed in Kabul and those processed in Kipkut in 2006-7. ($p = 0.01$)

There is no significant difference between the isolation rates in samples processed in Kipkut in 2006-7 and those processed in Kipkut in 2008 ($p = 0.617$)

3.3.2 Antibiotic susceptibility of isolates to various antibiotics

Tables 3.17 - 3.20 show the susceptibility of isolates of *Streptococcus pneumoniae* to various antibiotics as measured by the disc diffusion method.

Age in months by collection			Female					Male					Total		
2008	Sensitive	%	Resistant	%	**total**	Sensitive	%	Resistant	%	**total**	Sensitive	%	Resistant	%	**total**
0-11	11	*100*	0	*0*	**11**	6	*86*	1	*14*	**7**	**17**	***94***	**1**	***6***	**18**
12 – 23	24	*100*	0	*0*	**24**	15	*94*	1	*6*	**16**	**39**	***98***	**1**	***3***	**40**
24-35	19	*95*	1	*5*	**20**	17	*100*	0	*0*	**17**	**36**	***97***	**1**	***3***	**37**
36-47	8	*80*	2	*20*	**10**	9	*100*	0	*0*	**9**	**17**	***89***	**2**	***11***	**19**
48-59	2	*100*	0	*0*	**2**	6	*100*	0	*0*	**6**	**8**	***100***	**0**	***0***	**8**
60-71	3	*100*	0	*0*	**3**	1	*100*	0	*0*	**1**	**4**	***100***	**0**	***0***	**4**
more than 71	3	*100*	0	*0*	**3**	4	*100*	0	*0*	**4**	**7**	***100***	**0**	***0***	**7**
	70	*96*	3	*4*	**73**	58	*97*	2	*3*	**60**	**128**	***96***	**5**	***4***	**133**
2006															
0-11	5	*100*	0	*0*	**5**	4	*57*	3	*43*	**7**	**9**	***75***	**3**	***25***	**12**
12 – 23	8	*62*	5	*38*	**13**	3	*38*	5	*63*	**8**	**11**	***52***	**10**	***48***	**21**
24-35	4	*50*	4	*50*	**8**	8	*53*	7	*47*	**15**	**12**	***52***	**11**	***48***	**23**
36-47	6	*67*	3	*33*	**9**	4	*67*	2	*33*	**6**	**10**	***67***	**5**	***33***	**15**
48-59	3	*75*	1	*25*	**4**										
60-71															
more than 71						1	*100*	0	*0*	**1**	**1**	***100***	**0**	***0***	**1**
	26	*67*	13	*33*	**39**	20	*54*	17	*46*	**37**	**46**	***61***	**30**	***39***	**76**
2005															
0-11															
12 – 23	1	*100*	0	*0*	**1**	1	*33*	2	*67*	**3**	**2**	***50***	**2**	***50***	**4**
24-35						1	*100*	0	*0*	**1**	**1**	***100***	**0**	***0***	**1**
more than 36															
	1	*100*	0	*0*	**1**	2	*50*	2	*50*	**4**	**3**	***60***	**2**	***40***	**5**
totals															
0-11	16	*100*	0	*0*	**16**	10	*71*	4	*29*	**14**	**26**	***87***	**4**	***13***	**30**
12 – 23	33	*87*	5	*13*	**38**	19	*70*	8	*30*	**27**	**52**	***80***	**13**	***20***	**65**
24-35	23	*82*	5	*18*	**28**	26	*79*	7	*21*	**33**	**49**	***80***	**12**	***20***	**61**
36-47	14	*74*	5	*26*	**19**	13	*87*	2	*13*	**15**	**27**	***79***	**7**	***21***	**34**
48-59	5	*83*	1	*17*	**6**	6	*100*	0	*0*	**6**	**11**	***92***	**1**	***8***	**12**
60-71	3	*100*	0	*0*	**3**	1	*100*	0	*0*	**1**	**4**	***100***	**0**	***0***	**4**
more than 71	3	*100*	0	*0*	**3**	5	*100*	0	*0*	**5**	**8**	***100***	**0**	***0***	**8**
total	97	*86*	16	*14*	**113**	80	*79*	21	*21*	**101**	**177**	***83***	**37**	***17***	**214**

Table 3.17 sensitivity and resistance to oxacillin

	Female							Male							Total						
2008	Sensitive	%	Intermediate	%	Resistant	%	**total**	Sensitive	%	Intermediate	%	Resistant	%	**total**	Sensitive	%	Intermediate	%	Resistant	%	**total**
0-11	4	*36*	3	*27*	4	*36*	**11**	1	*14*	0	*0*	6	*86*	**7**	**5**	*28*	**3**	*17*	**10**	*56*	**18**
12 – 23	4	*17*	2	*8*	18	*75*	**24**	4	*25*	1	*6*	11	*69*	**16**	**8**	*20*	**3**	*8*	**29**	*73*	**40**
24-35	3	*15*	3	*15*	14	*70*	**20**	5	*29*	1	*6*	11	*65*	**17**	**8**	*22*	**4**	*11*	**25**	*68*	**37**
36-47	1	*10*	0	*0*	9	*90*	**10**	0	*0*	1	*11*	8	*89*	**9**	**1**	*5*	**1**	*5*	**17**	*89*	**19**
48-59	0	*0*	0	*0*	2	*100*	**2**	1	*17*	0	*0*	5	*83*	**6**	**1**	*13*	**0**	*0*	**7**	*88*	**8**
60-71	2	*67*	1	*33*	0	*0*	**3**	0	*0*	0	*0*	1	*100*	**1**	**2**	*50*	**1**	*25*	**1**	*25*	**4**
more than 71	0	*0*	1	*33*	2	*67*	**3**	0	*0*	1	*25*	3	*75*	**4**	**0**	*0*	**2**	*29*	**5**	*71*	**7**
total	14	*19*	10	*14*	49	*67*	**73**	11	*18*	4	*7*	45	*75*	**60**	**25**	*19*	**14**	*11*	**94**	*71*	**133**
2006																					
0-11	4	*80*	0	*0*	1	*20*	**5**	1	*14*	0	*0*	6	*86*	**7**	**5**	*42*	**0**	*0*	**7**	*58*	**12**
12 – 23	3	*23*	0	*0*	10	*77*	**13**	2	*25*	1	*13*	5	*63*	**8**	**5**	*24*	**1**	*5*	**15**	*71*	**21**
24-35	3	*38*	0	*0*	5	*63*	**8**	2	*13*	1	*7*	12	*80*	**15**	**5**	*22*	**1**	*4*	**17**	*74*	**23**
36-47	1	*11*	1	*11*	7	*78*	**9**	2	*33*	1	*17*	3	*50*	**6**	**3**	*20*	**2**	*13*	**10**	*67*	**15**
48-59	2	*50*	1	*25*	1	*25*	**4**														
60-71			0		0																
more than 71			0		0			0	*0*	0	*0*	1	*100*	**1**	**0**	*0*	**0**	*0*	**1**	*100*	**1**
total	13	*33*	2	*5*	24	*62*	**39**	7	*19*	3	*8*	27	*73*	**37**	**20**	*26*	**5**	*7*	**51**	*67*	**76**
2005																					
0-11																					
12 – 23	0	*0*	0		1	*100*	**1**	0	*0*	0	*0*	3	*100*	**3**	**0**	*0*	**0**	*0*	**4**	*100*	**4**
24-35								0	*0*	0	*0*	1	*100*	**1**	**0**	*0*	**0**	*0*	**1**	*100*	**1**
more than 36																					
total	0	*0*	0		1	*100*	**1**	0	*0*	0	*0*	4	*100*	**4**	**0**	*0*	**0**	*0*	**5**	*100*	**5**
totals																					
0-11	8	*50*	3	*19*	5	*31*	**16**	2	*14*	0	*0*	12	*86*	**14**	**10**	*33*	**3**	*10*	**17**	*57*	**30**
12 – 23	7	*18*	2	*5*	29	*76*	**38**	6	*22*	2	*7*	19	*70*	**27**	**13**	*20*	**4**	*6*	**48**	*74*	**65**
24-35	6	*21*	3	*11*	19	*68*	**28**	7	*21*	2	*6*	24	*73*	**33**	**13**	*21*	**5**	*8*	**43**	*70*	**61**
36-47	2	*11*	1	*5*	16	*84*	**19**	2	*13*	2	*13*	11	*73*	**15**	**4**	*12*	**3**	*9*	**27**	*79*	**34**
48-59	2	*33*	1	*17*	3	*50*	**6**	1	*17*	0	*0*	5	*83*	**6**	**3**	*25*	**1**	*8*	**8**	*67*	**12**
60-71	2	*67*	1	*33*	0	*0*	**3**	0	*0*	0	*0*	1	*100*	**1**	**2**	*50*	**1**	*25*	**1**	*25*	**4**
more than 71	0	*0*	1	*33*	2	*67*	**3**	0	*0*	1	*20*	4	*80*	**5**	**0**	*0*	**2**	*25*	**6**	*75*	**8**
total	27	*24*	12	*11*	74	*65*	**113**	18	*18*	7	*7*	76	*75*	**101**	**45**	*21*	**19**	*9*	**150**	*70*	**214**

Table 3.18 sensitivity and resistance to co-trimoxazole

	Female							Male							Total						
2008	Sensitive	%	Intermediate	%	Resistant	%	**total**	Sensitive	%	Intermediate	%	Resistant	%	**total**	Sensitive	%	Intermediate	%	Resistant	%	**total**
0-11	10	*91*	0	*0*	1	*9*	**11**	5	*71*	0	*0*	2	*29*	**7**	**15**	*83*	**0**	*0*	**3**	*17*	**18**
12 – 23	20	*83*	1	*4*	3	*13*	**24**	16	*100*	0	*0*	0	*0*	**16**	**36**	*90*	**1**	*3*	**3**	*8*	**40**
24-35	18	*90*	1	*5*	1	*5*	**20**	14	*82*	1	*6*	2	*12*	**17**	**32**	*86*	**2**	*5*	**3**	*8*	**37**
36-47	10	*100*	0	*0*	0	*0*	**10**	8	*89*	0	*0*	1	*11*	**9**	**18**	*95*	**0**	*0*	**1**	*5*	**19**
48-59	1	*50*	1	*50*	0	*0*	**2**	5	*83*	0	*0*	1	*17*	**6**	**6**	*75*	**1**	*13*	**1**	*13*	**8**
60-71	3	*100*	0	*0*	0	*0*	**3**	1	*100*	0	*0*	0	*0*	**1**	**4**	*100*	**0**	*0*	**0**	*0*	**4**
more than 71	2	*67*	0	*0*	1	*33*	**3**	4	*100*	0	*0*	0	*0*	**4**	**6**	*86*	**0**	*0*	**1**	*14*	**7**
total	**64**	***88***	3	***4***	6	***8***	**73**	53	*88*	1	*2*	6	*10*	**60**	**117**	*88*	**4**	*3*	**12**	*9*	**133**
2006																					
0-11	5	*100*	0	*0*	0	*0*	**5**	7	*100*	0	*0*	0	*0*	**7**	**12**	*100*	**0**	*0*	**0**	*0*	**12**
12 – 23	13	*100*	0	*0*	0	*0*	**13**	6	*75*	1	*13*	1	*13*	**8**	**19**	*90*	**1**	*5*	**1**	*5*	**21**
24-35	7	*88*	0	*0*	1	*13*	**8**	12	*80*	0	*0*	3	*20*	**15**	**19**	*83*	**0**	*0*	**4**	*17*	**23**
36-47	6	*67*	1	*11*	2	*22*	**9**	5	*83*	1	*17*	0	*0*	**6**	**11**	*73*	**2**	*13*	**2**	*13*	**15**
48-59	4	*100*	0	*0*	0	*0*	**4**														
60-71																					
more than 71								1	*100*	0	*0*	0	*0*	**1**	**1**	*100*	**0**	*0*	**0**	*0*	**1**
total	**35**	***90***	1	***3***	3	***8***	**39**	31	*84*	2	*5*	4	*11*	**37**	**66**	*87*	**3**	*4*	**7**	*9*	**76**
2005																					
0-11																					
12 – 23	1	*100*	0	*0*	0	*0*	**1**	3	*100*	0	*0*	0	*0*	**3**	**4**	*100*	**0**	*0*	**0**	*0*	**4**
24-35								1	*100*	0	*0*	0	*0*	**1**	**1**	*100*	**0**	*0*	**0**	*0*	**1**
more than 36																					
total	**1**	***100***	0	***0***	0	***0***	**1**	4	*100*	0	*0*	0	*0*	**4**	**5**	*100*	**0**	*0*	**0**	*0*	**5**
totals																					
0-11	15	*94*	0	*0*	1	*6*	**16**	12	*86*	0	*0*	2	*14*	**14**	**27**	*90*	**0**	*0*	**3**	*10*	**30**
12 – 23	34	*89*	1	*3*	3	*8*	**38**	25	*93*	1	*4*	1	*4*	**27**	**59**	*91*	**2**	*3*	**4**	*6*	**65**
24-35	25	*89*	1	*4*	2	*7*	**28**	27	*82*	1	*3*	5	*15*	**33**	**52**	*85*	**2**	*3*	**7**	*11*	**61**
36-47	16	*84*	1	*5*	2	*11*	**19**	13	*87*	1	*7*	1	*7*	**15**	**29**	*85*	**2**	*6*	**3**	*9*	**34**
48-59	5	*83*	1	*17*	0	*0*	**6**	5	*83*	0	*0*	1	*17*	**6**	**10**	*83*	**1**	*8*	**1**	*8*	**12**
60-71	3	*100*	0	*0*	0	*0*	**3**	1	*100*	0	*0*	0	*0*	**1**	**4**	*100*	**0**	*0*	**0**	*0*	**4**
more than 71	2	*67*	0	*0*	1	*33*	**3**	5	*100*	0	*0*	0	*0*	**5**	**7**	*88*	**0**	*0*	**1**	*13*	**8**
total	100	*88*	4	*4*	9	*8*	**113**	88	*87*	3	*3*	10	*10*	**101**	**188**	*88*	**7**	*3*	**19**	*9*	**214**

Table 3.19 sensitivity and resistance to erythromycin

	Female							Male							Total						
2008	Sensitive	%	Intermediate	%	Resistant	%	**total**	Sensitive	%	Intermediate	%	Resistant	%	**total**	Sensitive	%	Intermediate	%	Resistant	%	**total**
0-11	10	*91*	0	*0*	1	*9*	**11**	3	*43*	0	*0*	4	*57*	**7**	**13**	*72*	**0**	*0*	**5**	*28*	**18**
12 – 23	13	*54*	1	*4*	10	*42*	**24**	10	*63*	0	*0*	6	*38*	**16**	**23**	*58*	**1**	*3*	**16**	*40*	**40**
24-35	9	*45*	1	*5*	10	*50*	**20**	9	*53*	1	*6*	7	*41*	**17**	**18**	*49*	**2**	*5*	**17**	*46*	**37**
36-47	5	*50*	0	*0*	5	*50*	**10**	5	*56*	0	*0*	4	*44*	**9**	**10**	*53*	**0**	*0*	**9**	*47*	**19**
48-59	1	*50*	0	*0*	1	*50*	**2**	2	*33*	0	*0*	4	*67*	**6**	**3**	*38*	**0**	*0*	**5**	*63*	**8**
60-71	3	*100*	0	*0*	0	*0*	**3**	0	*0*	0	*0*	1	*100*	**1**	**3**	*75*	**0**	*0*	**1**	*25*	**4**
more than 71	1	*33*	0	*0*	2	*67*	**3**	4	*100*	0	*0*	0	*0*	**4**	**5**	*71*	**0**	*0*	**2**	*29*	**7**
total	**42**	***58***	2	***3***	29	***40***	**73**	33	*55*	1	*2*	26	*43*	**60**	**75**	*56*	**3**	*2*	**55**	*41*	**133**
2006																					
0-11	4	*80*	0	*0*	1	*20*	**5**	4	*57*	0	*0*	3	*43*	**7**	**8**	*67*	**0**	*0*	**4**	*33*	**12**
12 – 23	6	*46*	3	*23*	4	*31*	**13**	3	*38*	1	*13*	4	*50*	**8**	**9**	*43*	**4**	*19*	**8**	*38*	**21**
24-35	6	*75*	0	*0*	2	*25*	**8**	9	*60*	0	*0*	6	*40*	**15**	**15**	*65*	**0**	*0*	**8**	*35*	**23**
36-47	4	*44*	1	*11*	4	*44*	**9**	3	*50*	1	*17*	2	*33*	**6**	**7**	*47*	**2**	*13*	**6**	*40*	**15**
48-59	1	*25*	0	*0*	3	*75*	**4**														
60-71																					
more than 71								1	*100*	0	*0*	0	*0*	**1**	**1**	*100*	**0**	*0*	**0**	*0*	**1**
total	**21**	***54***	4	***10***	14	***36***	**39**	20	*54*	2	*5*	15	*41*	**37**	**41**	*54*	**6**	*8*	**29**	*38*	**76**
2005																					
0-11																					
12 – 23	1	*100*	0	*0*	0	*0*	**1**	1	*33*	0	*0*	2	*67*	**3**	**2**	*50*	**0**	*0*	**2**	*50*	**4**
24-35								1	*100*	0	*0*	0	*0*	**1**	**1**	*100*	**0**	*0*	**0**	*0*	**1**
more than 36																					
total	**1**	***100***	0	***0***	0	***0***	**1**	2	*50*	0	*0*	0	*0*	**4**	**3**	*60*	**0**	*0*	**2**	*40*	**5**
totals																					
0-11	14	*88*	0	*0*	2	*13*	**16**	7	*50*	0	*0*	7	*50*	**14**	**21**	*70*	**0**	*0*	**9**	*30*	**30**
12 – 23	20	*53*	4	*11*	14	*37*	**38**	14	*52*	1	*4*	12	*44*	**27**	**34**	*52*	**5**	*8*	**26**	*40*	**65**
24-35	15	*54*	1	*4*	12	*43*	**28**	19	*58*	1	*3*	13	*39*	**33**	**34**	*56*	**2**	*3*	**25**	*41*	**61**
36-47	9	*47*	1	*5*	9	*47*	**19**	8	*53*	1	*7*	6	*40*	**15**	**17**	*50*	**2**	*6*	**15**	*44*	**34**
48-59	2	*33*	0	*0*	4	*67*	**6**	2	*33*	0	*0*	4	*67*	**6**	**4**	*33*	**0**	*0*	**8**	*67*	**12**
60-71	3	*100*	0	*0*	0	*0*	**3**	0	*0*	0	*0*	1	*100*	**1**	**3**	*75*	**0**	*0*	**1**	*25*	**4**
more than 71	1	*33*	0	*0*	2	*67*	**3**	5	*100*	0	*0*	0	*0*	**5**	**6**	*75*	**0**	*0*	**2**	*25*	**8**
total	66	*58*	6	*5*	41	*36*	**113**	55	*54*	3	*3*	43	*43*	**101**	**119**	*56*	**9**	*4*	**86**	*40*	**214**

Table 3.20 sensitivity and resistance to tetracycline

Table 3.21 Shows a summary of sensitivity and resistance by year and antibiotic

2008	PEN	%	SXT	%	ERY	%	TET	%
Resistant	5	*96*	94	*71*	12	*9*	55	*41*
Intermediate			13	*10*	4	*3*	3	*2*
Sensitive	128	*4*	26	*20*	117	*88*	75	*56*
total	133		133		133		133	
2006								
Resistant	30	*39*	51	*63*	7	*8*	29	*38*
Intermediate			5	*8*	3	*4*	6	*8*
Sensitive	46	*59*	20	*28*	66	*84*	41	*54*
total	76		76		76		76	
2005								
Resistant	2	*40*	5	*100*	0	*0*	2	*40*
Intermediate			0	*0*	0	*0*	0	*0*
Sensitive	3	*60*	0	*0*	5	*100*	3	*60*
total	5		5		5		5	
total								
Sensitive	177	*83*	46	*21*	188	*88*	119	*56*
Intermediate			18	*8*	7	*3*	9	*4*
Resistant	37	*17*	150	*70*	19	*9*	86	*40*
total	214		214		214		214	

Table 3.21 Summary of sensitivity and resistance by year and antibiotic

A chi squared 2 way contingency calculation using http://statpages.org/ctab2x2 was performed, comparing rate of resistance to each antibiotic in 2006-7, with resistance rate to each in 2008 for all ages together, and rate of (resistant + intermediate sensitivity) to each antibiotic in 2006-7, with rate of (resistant + intermediate sensitivity) to each in 2008 for all ages and both sexes together

For oxacillin:

(resistant from total number of isolates 2006-7) vs (resistant from total number of isolates 2008), $p = 0.000$

For co-trimoxazole

(resistant + intermediate sensitivity from total number of isolates 2006-7) vs (resistant + intermediate sensitivity from total number of isolates 2008) p = 0.256

(resistant from total number of isolates 2006-7) vs (resistant from total number of isolates 2008) p = 0.590

For erythromycin

(resistant + intermediate sensitivity from total number of isolates 2006-7) vs (resistant + intermediate sensitivity from total number of isolates 2008) p = 0.812

(resistant from total number of isolates 2006-7) vs (resistant from total number of isolates 2008) p = 0.938

For tetracycline

(resistant + intermediate sensitivity from total number of isolates 2006-7) vs (resistant + intermediate sensitivity from total number of isolates 2008) p = 0.732

(resistant from total number of isolates 2006-7) vs (resistant from total number of isolates 2008) p = 0.650

There is a significant difference between rates of resistance to oxacillin in samples collected in 2006-7 and samples collected in 2008.

Charts 3.8 - 3.15 show zone sizes, by year and numbers of isolates, and percentages of zone sizes, for each of four antibiotics, oxacillin, co-trimoxazole, erythromycin and tetracycline.

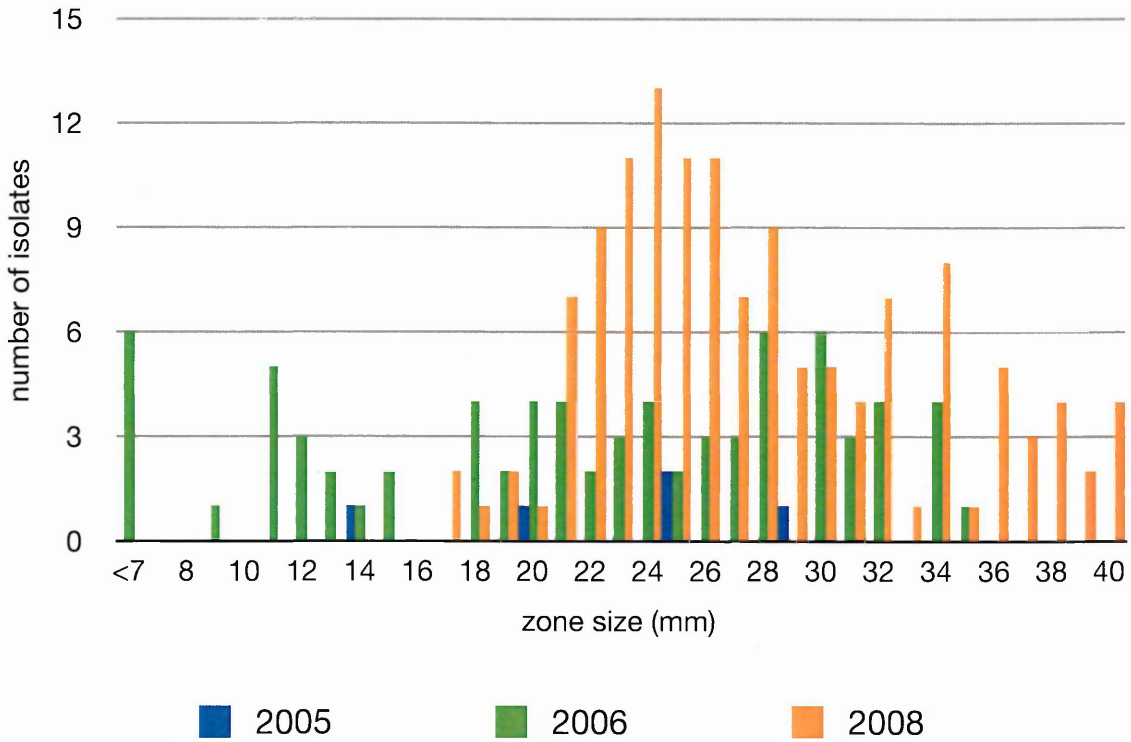
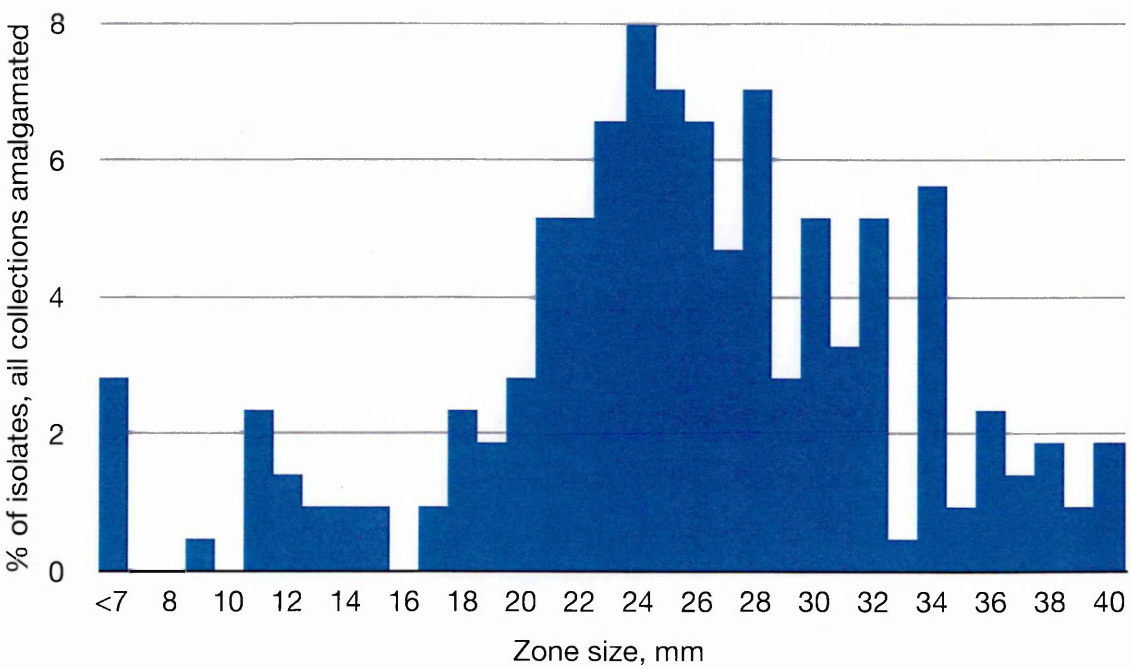


Chart 3.8 Zone sizes for oxacillin, by number of isolates of *Streptococcus pneumoniae*



A zone size of less than 7mm indicated that the bacterial lawn grew to the edge of the antibiotic disc. This applies to all such charts in this section.

Chart 3.9 Zone sizes for oxacillin, by percentage of isolates of *Streptococcus pneumoniae*, all collections amalgamated

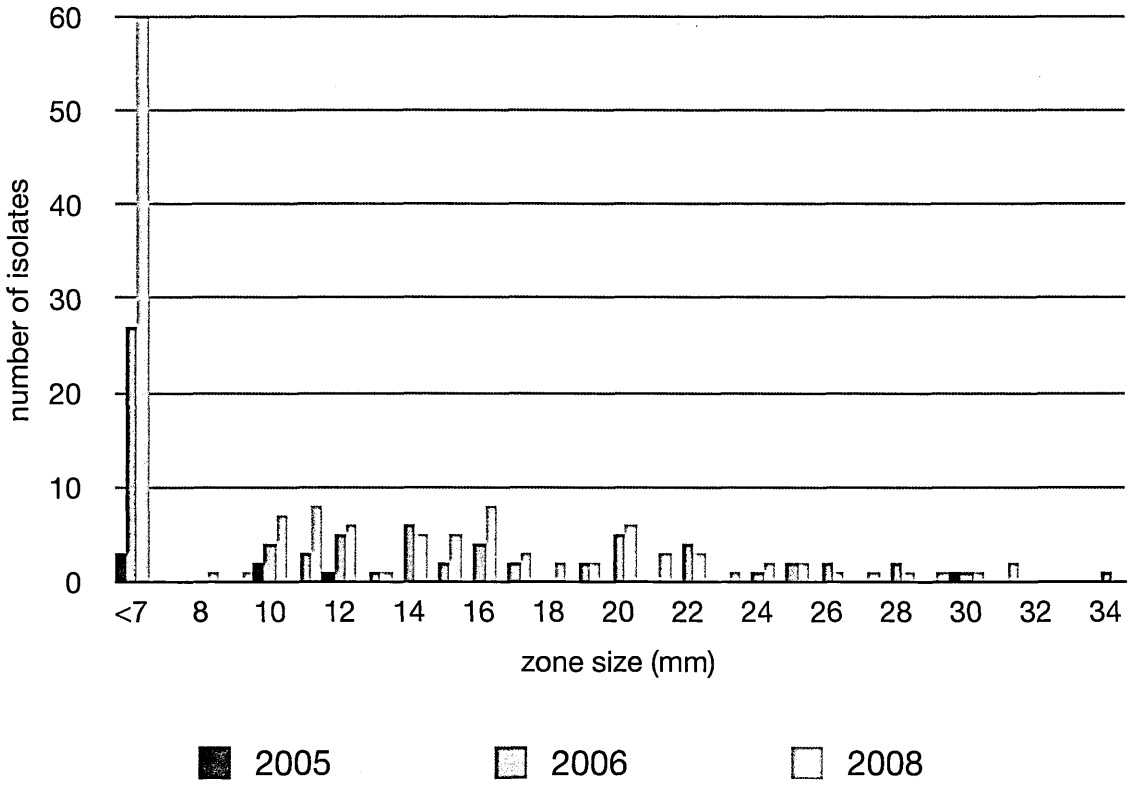


Chart 3.10 Zone sizes for co-trimoxazole, by number of isolates of *Streptococcus pneumoniae*

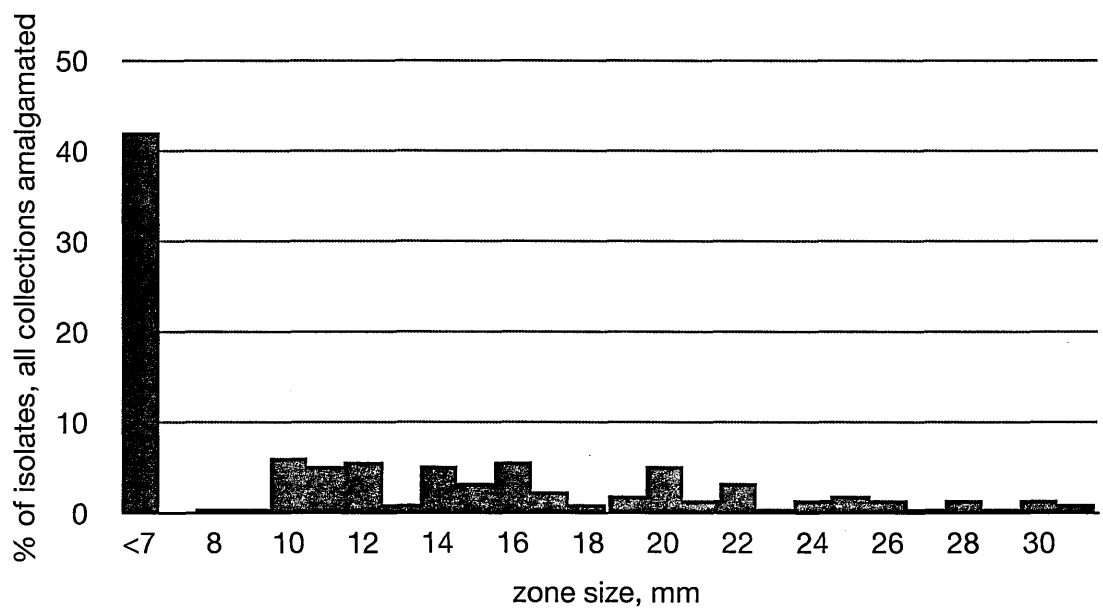


Chart 3.11 Zone sizes for co-trimoxazole by percentage of isolates of *Streptococcus pneumoniae*, all collections amalgamated

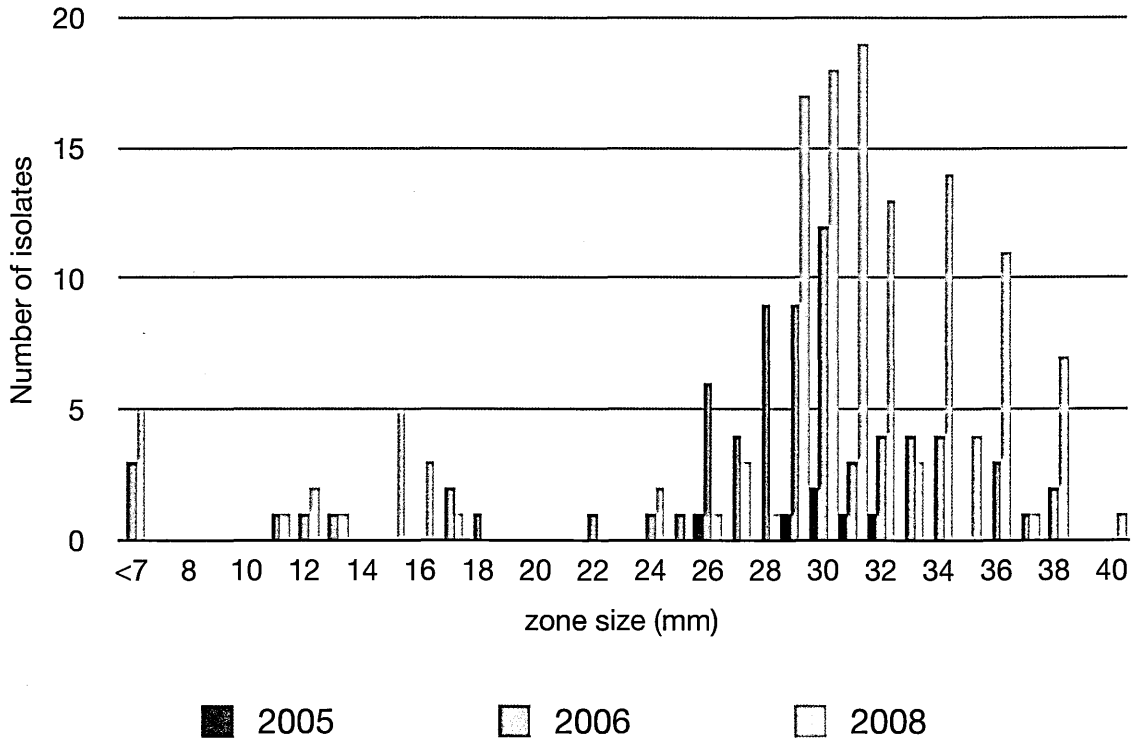


Chart 3.12 Zone sizes for erythromycin, by number of isolates of *Streptococcus pneumoniae*

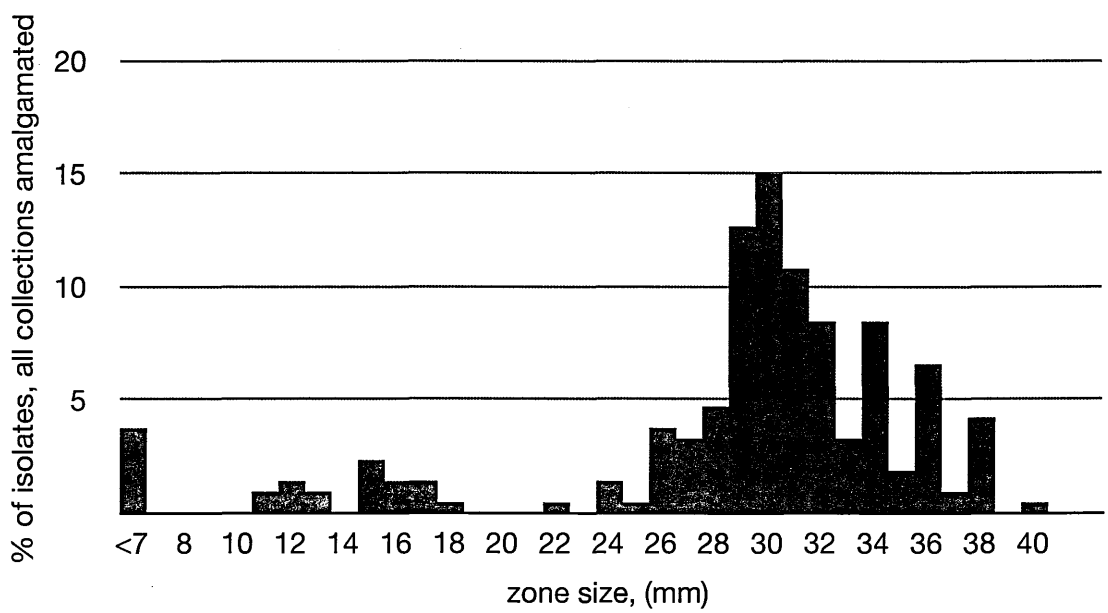


Chart 3.13 Zone sizes for erythromycin, by percentage of isolates of *Streptococcus pneumoniae*, all collections amalgamated.

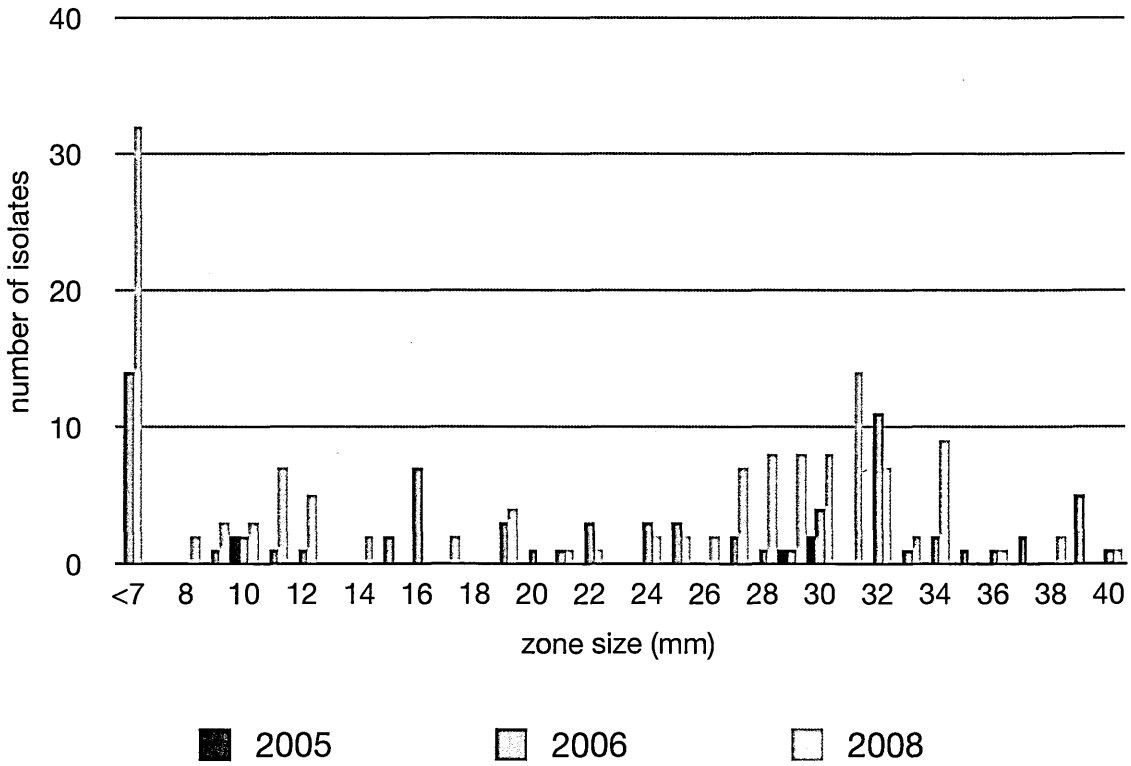


Chart 3.14 Zone sizes for tetracycline, by number of isolates of *Streptococcus pneumoniae*

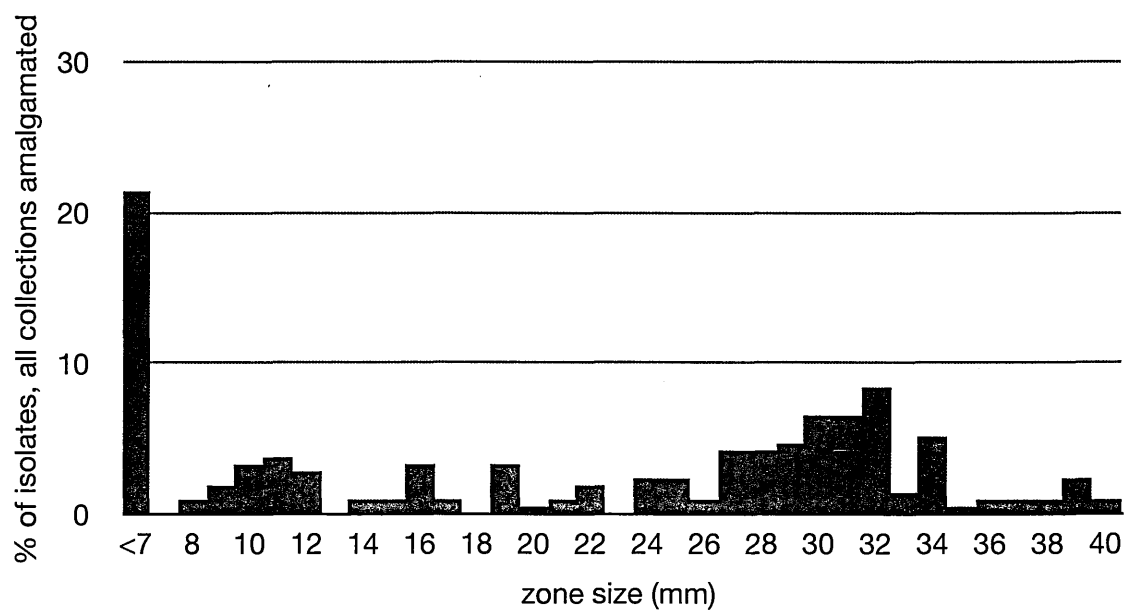


Chart 3.15 Zone sizes for tetracycline, by percentage of isolates of *Streptococcus pneumoniae*, all collections amalgamated

3.3.3 Multiple resistances

Table 3.22 shows the numbers of isolates of *Streptococcus pneumoniae*, showing single and multiple resistance in their combinations.

		2006	%	2008	%	total	%
fully susceptible		11	*14*	23	*17*	34	16
resistance to only	Erythromycin (ERY)	0	*0*	0	*0*	0	0
	Co-trimoxazole (SXT)	24	*32*	52	*39*	76	36
	Oxacillin (OX)	3	*4*	0	*0*	3	1
	Tetracycline (TET)	4	*5*	15	*11*	19	9
resistance to 2 discs	SXT/TET	5	*7*	25	*19*	30	14
	SXT/OX	9	*12*	1	*1*	10	5
	TET/OX	6	*8*	0	*0*	6	3
	ERY/SXT	0	*0*	2	*2*	2	1
	TET/ERY	0	*0*	1	*1*	1	0
resistance to 3 discs	SXT/TET/OX	8	*11*	3	*2*	11	5
	SXT/TET/ERY	1	*1*	9	*7*	10	5
	TET/ERY/OX	1	*1*			1	0
resistance to 4 discs	SXT/ERY/TET/OX	4	*5*	2	*2*	6	3
		76		133		209	

Table 3.22 Numbers of isolates of *Streptococcus pneumoniae*, showing single and multiple resistance in their combinations.

Table 3.23 shows the paired combinations of multiple reduced susceptibilities

	2006	%	2008	%	*p value for change*
total no isolates	76		133		
resistance to OX and ERY	5	*7*	2	*2*	p=0.05
resistance to OX and SXT	21	*28*	6	*5*	p=<0.0001
resistance to OX and TET	19	*25*	5	*4*	p=<0.0001
resistance to SXT and ERY	5	*7*	13	*10*	p= 0.609
resistance to SXT and TET	18	*24*	39	*29*	p=0.379
resistance to ERY and TET	6	*8*	5	*4*	p=0.198

Table 3.23 Paired combinations of multiple resistance

3.3.4 Minimum inhibitory concentrations

Charts 3.16 to 3.18 show the minimum inhibitory concentration of isolates with a disc diffusion zone size less than the standard breakpoint for penicillin, trimethoprim and tetracycline.

The x axes on these charts represent the graduations on the E-test strips.

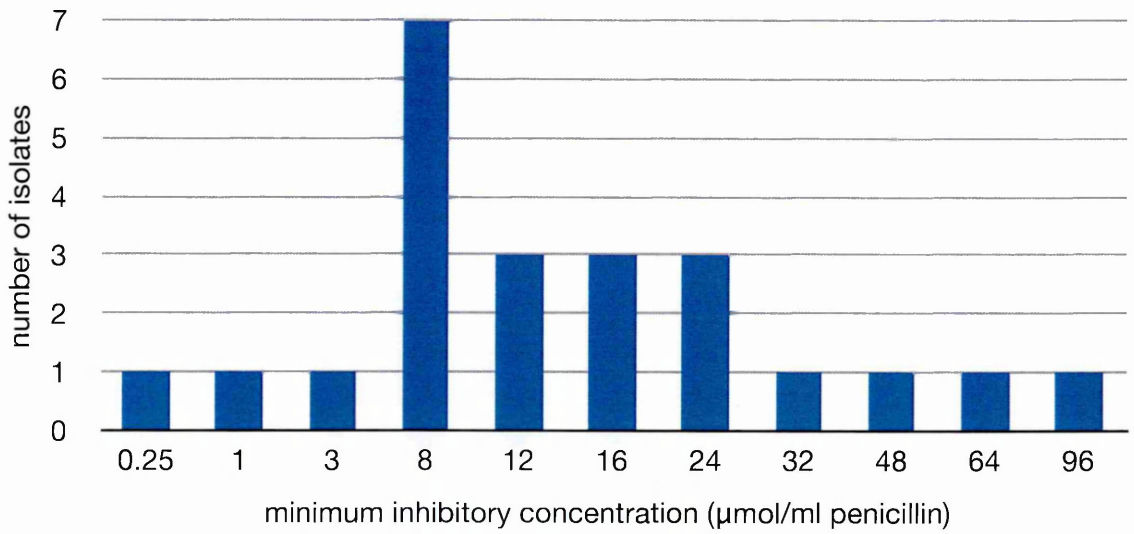


Chart 3.16 Minimum inhibitory concentration in isolates of *Streptococcus pneumoniae* with resistance to oxacillin on disc diffusion (MIC by E-Test penicillin strip)

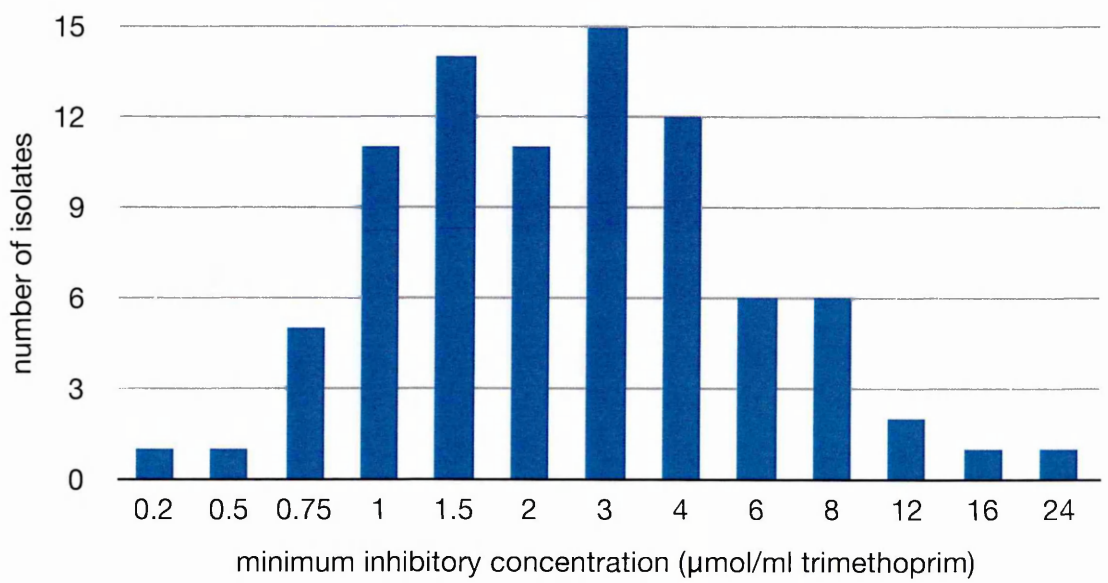


Chart 3.17 Minimum inhibitory concentration of trimethoprim by E-test in isolates of *Streptococcus pneumoniae* with resistance to co-trimoxazole on disc diffusion

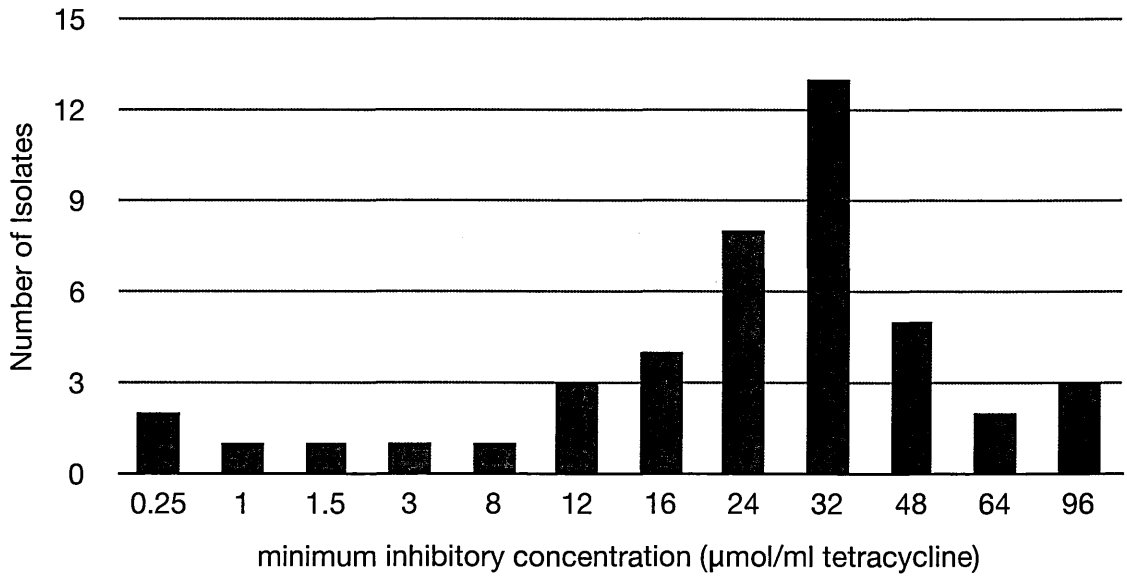
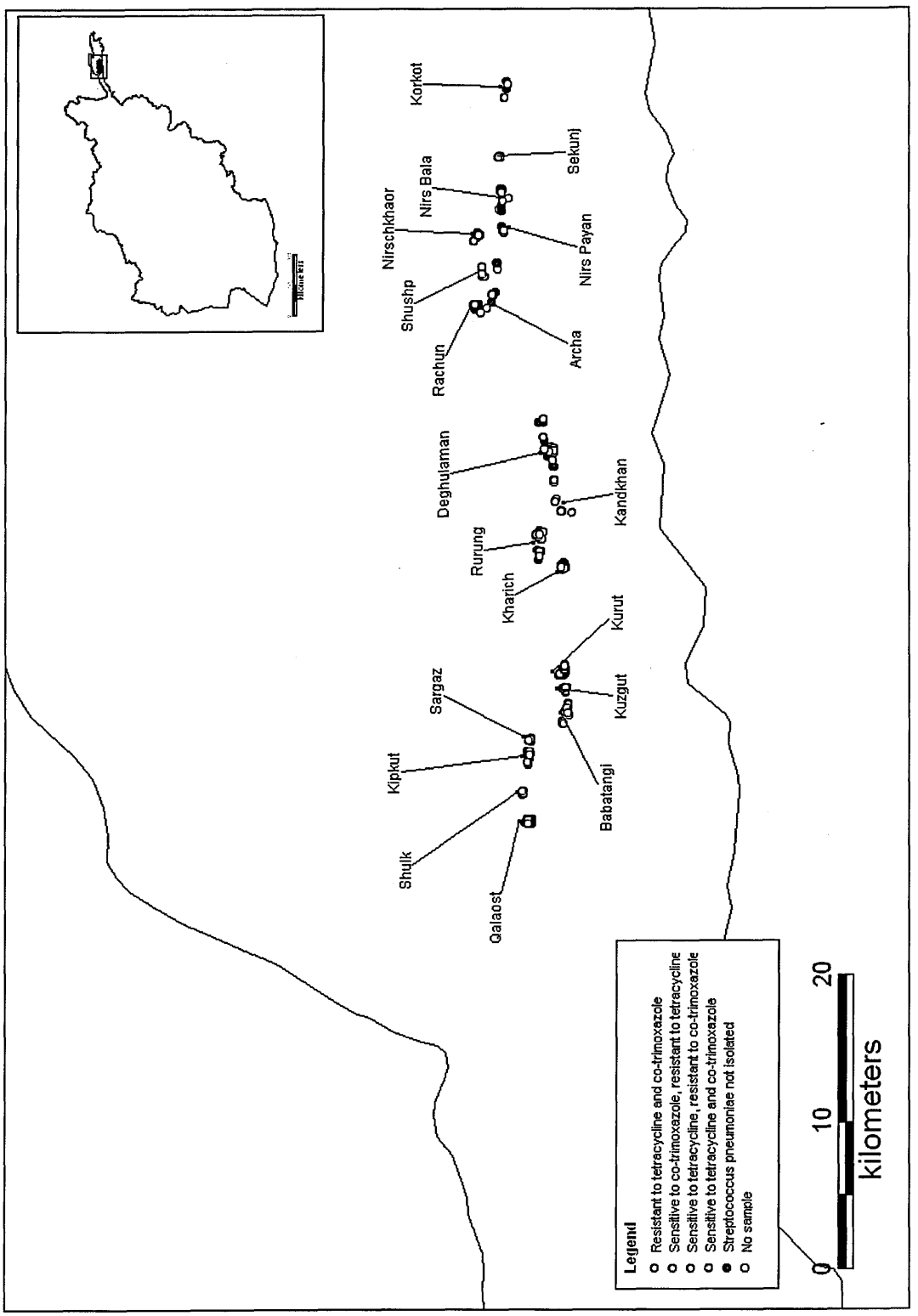


Chart 3.18 Minimum inhibitory concentration in isolates of *Streptococcus pneumoniae* with resistance to tetracycline.

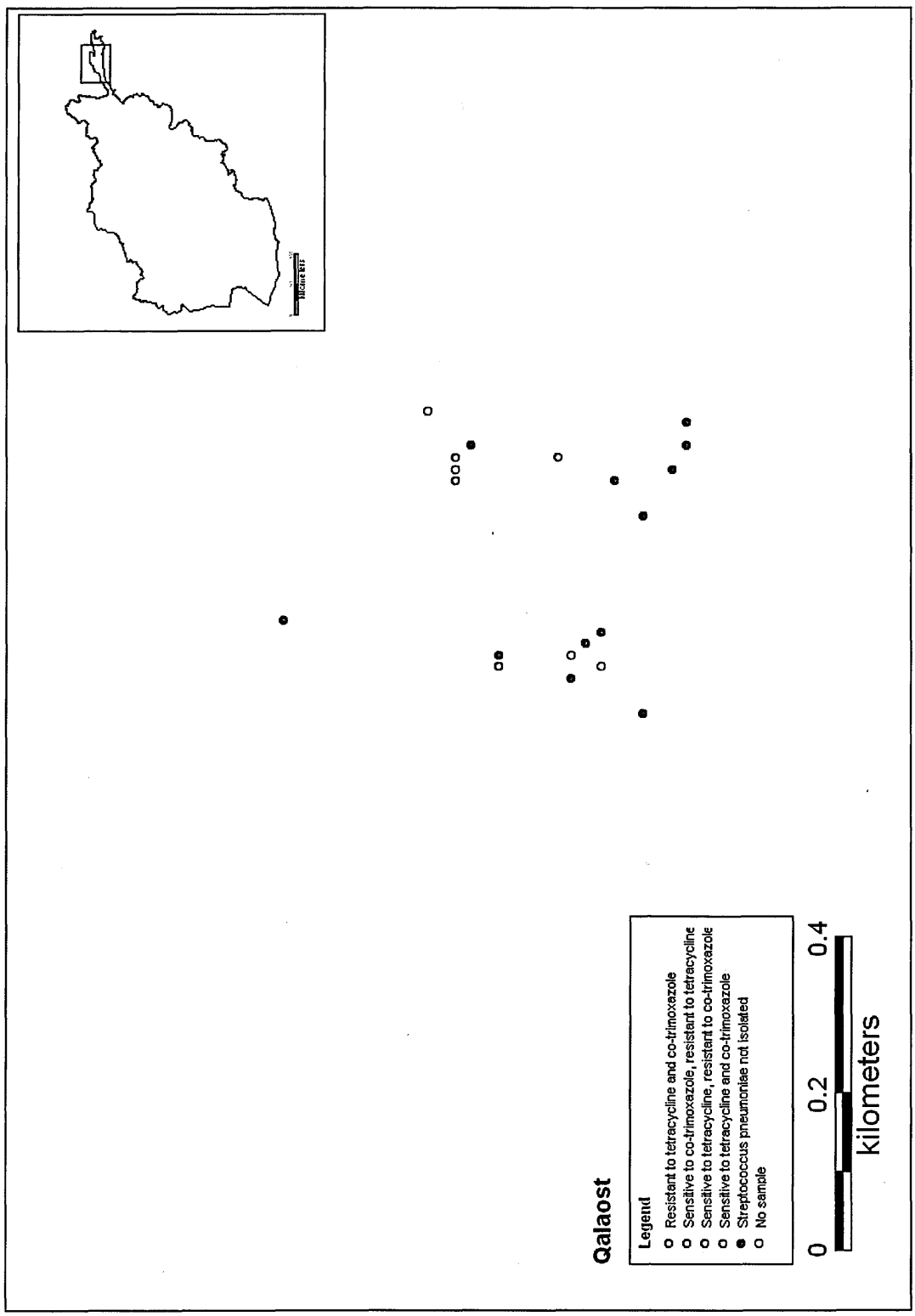
3.3.5 Geographical distribution

The following pages show maps of each village, with distribution of isolates.

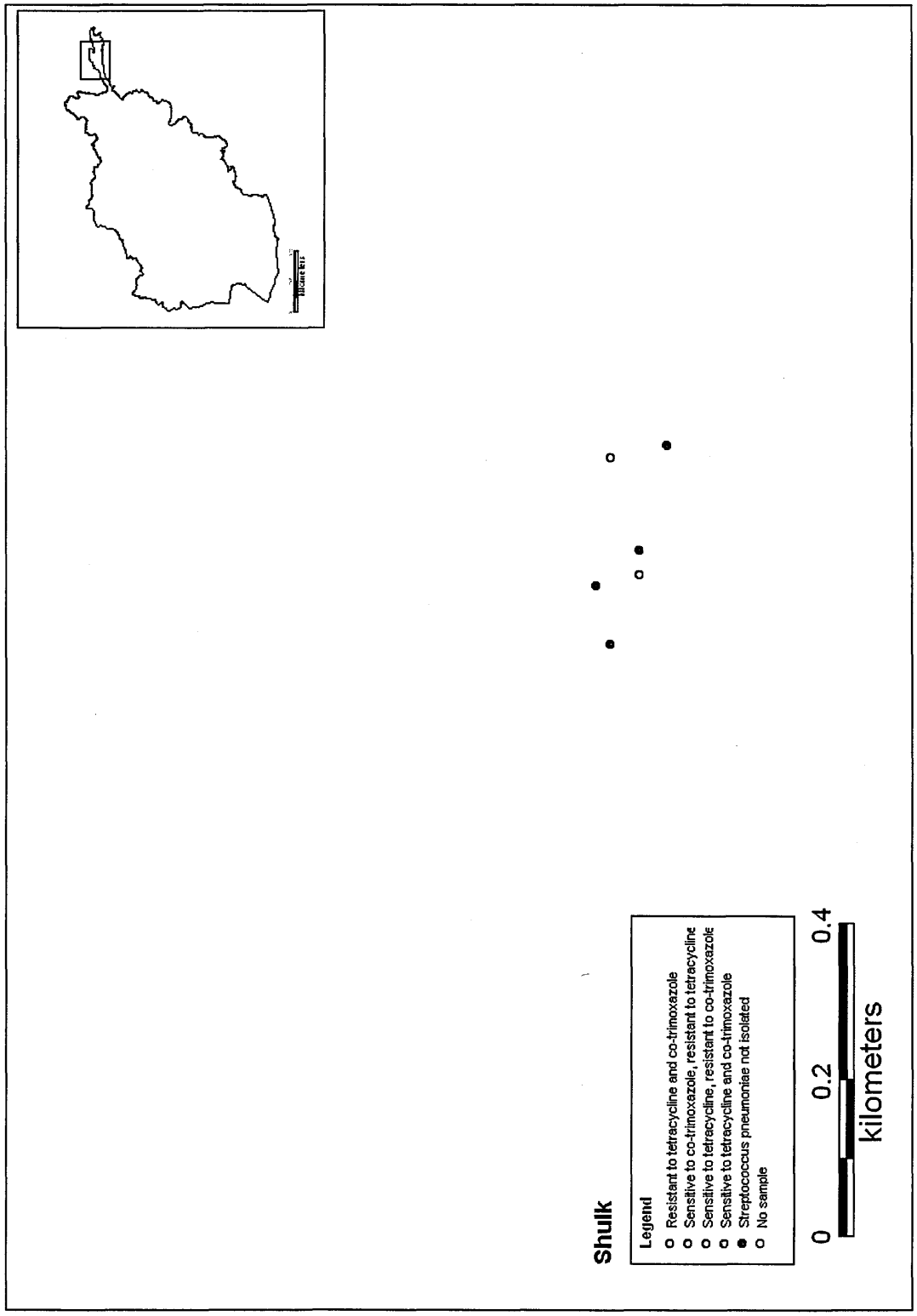
Map 3.1 Distribution of villages studied



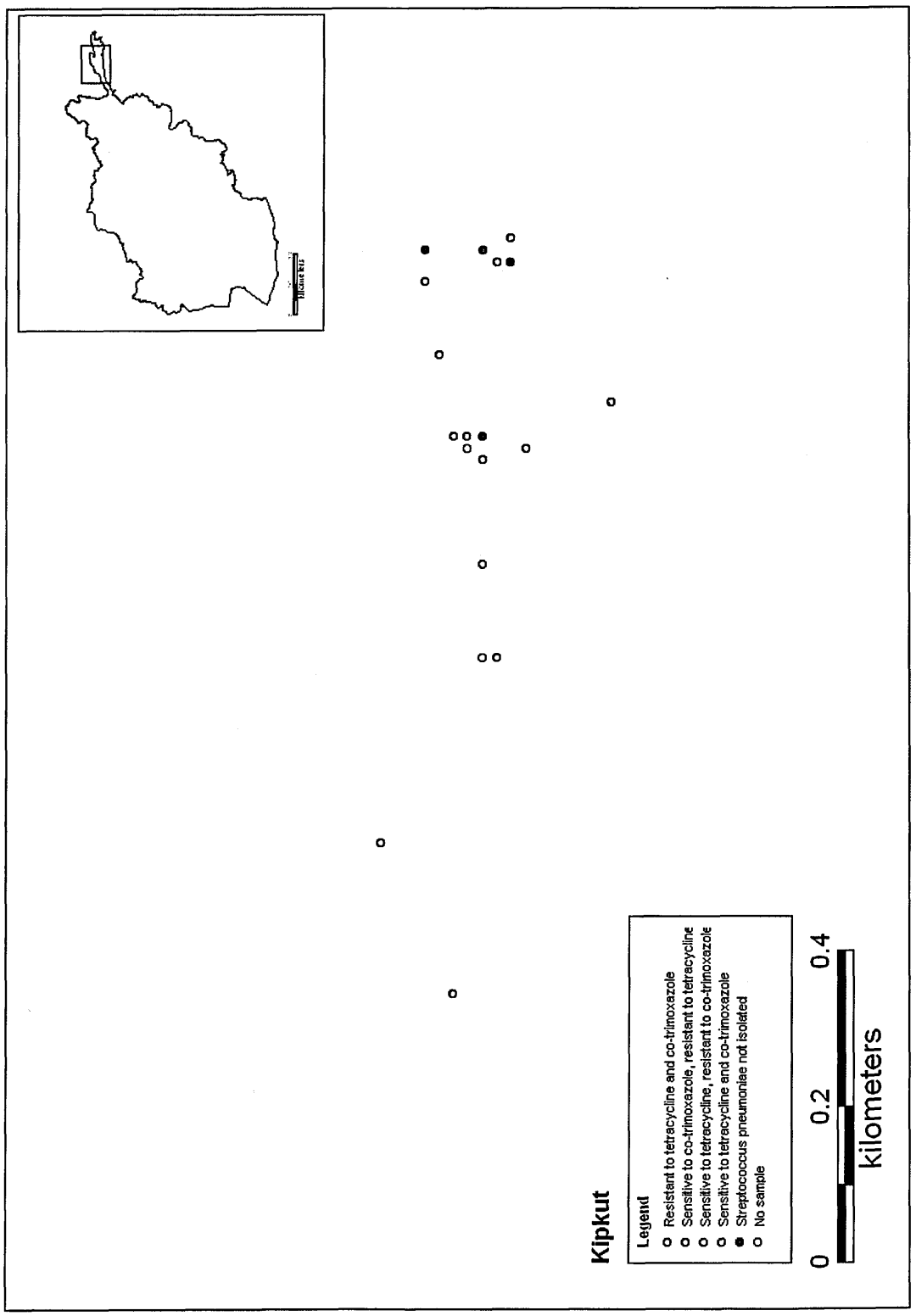
Map 3.2 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Qalaost



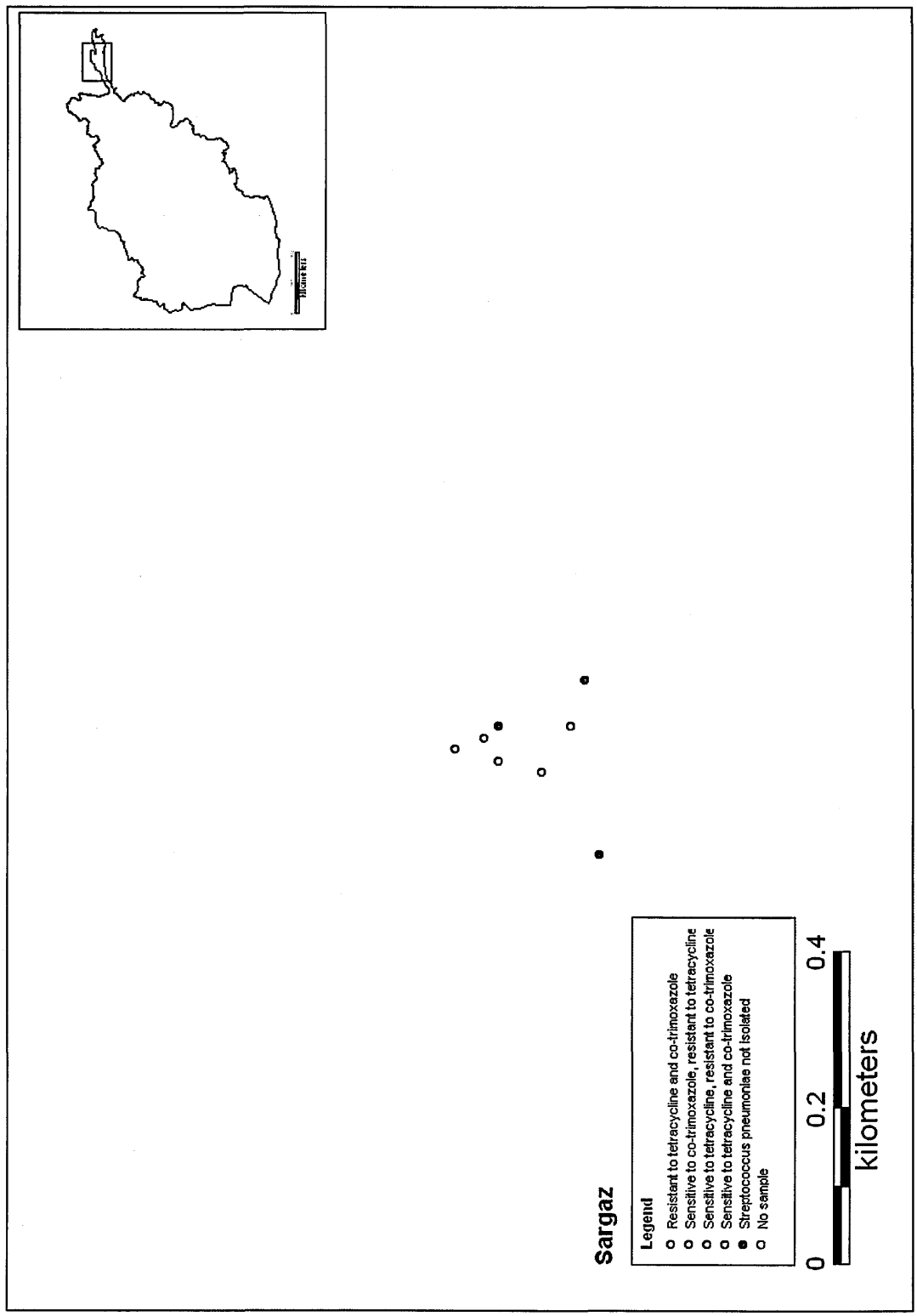
Map 3.3 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Shulk.



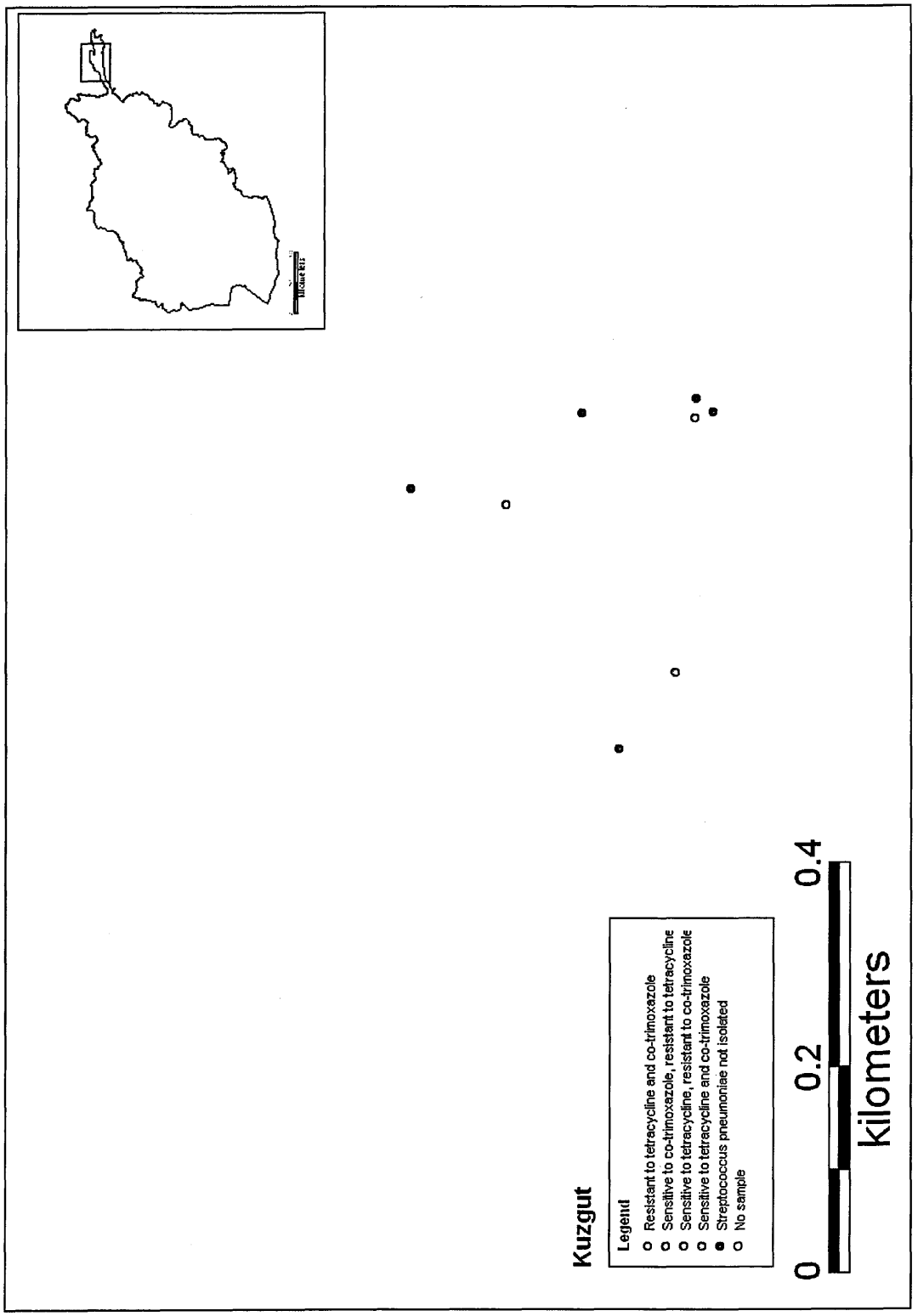
Map 3.4 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Kipkut.



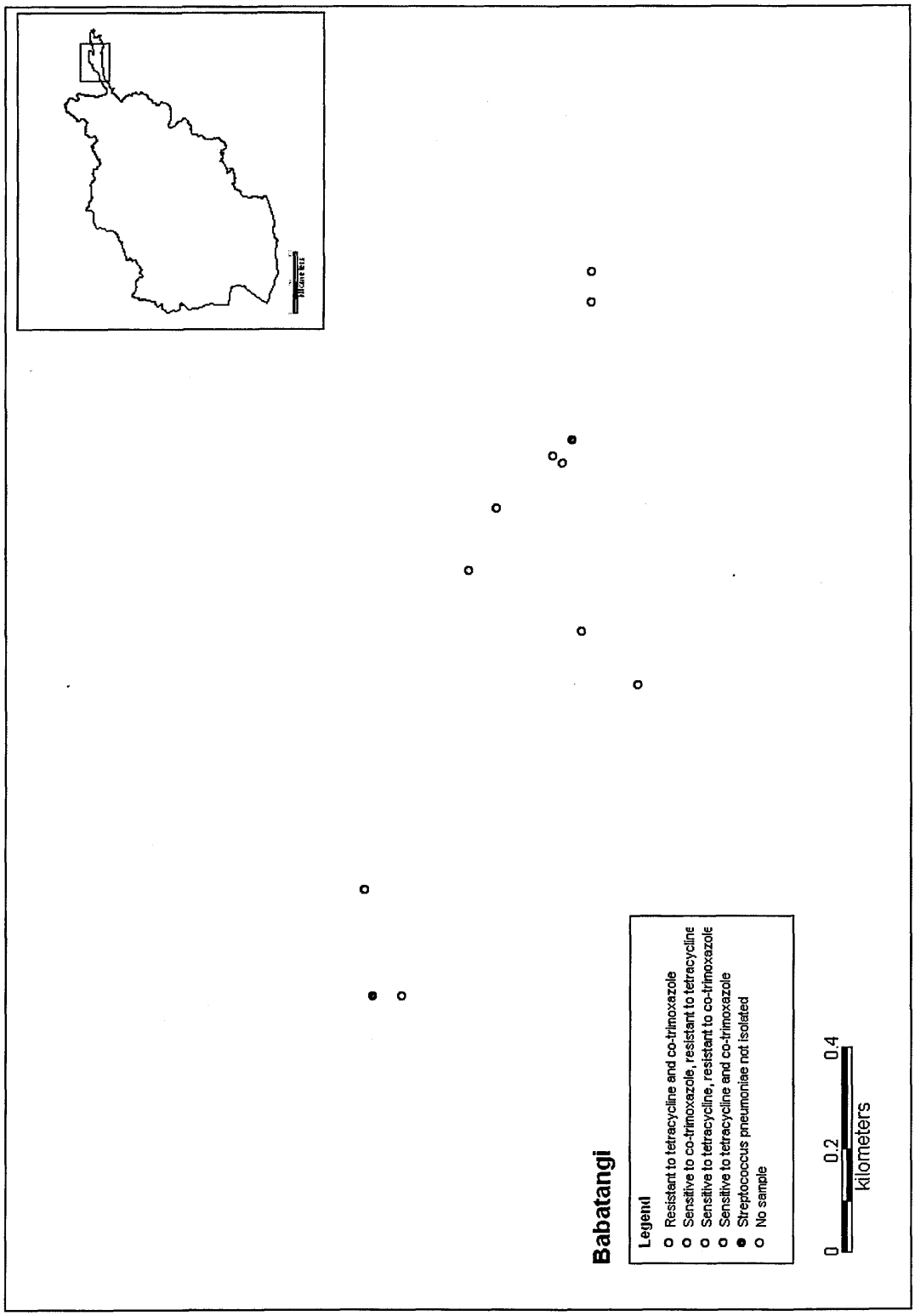
Map 3.5 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Sargaz.



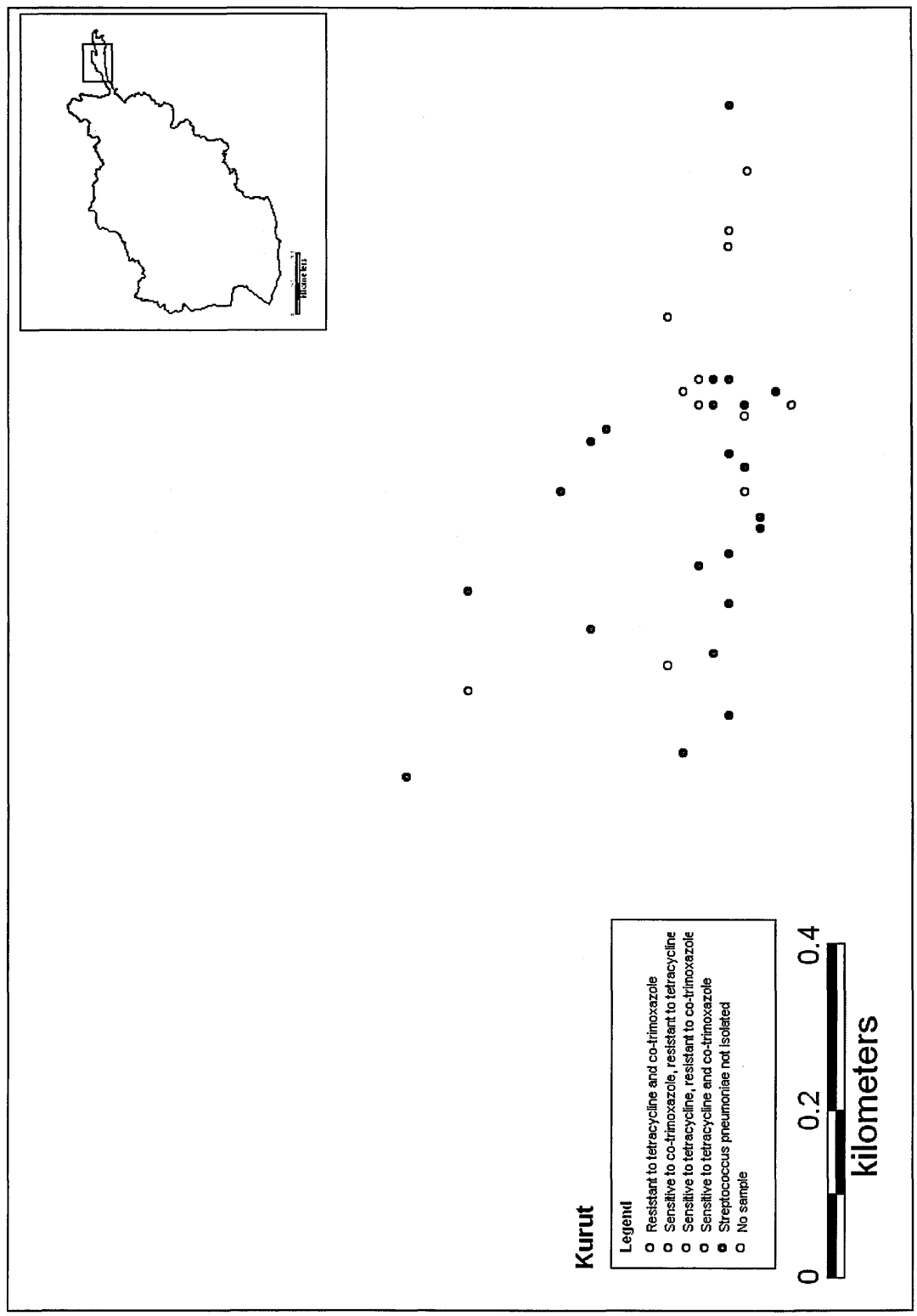
Map 3.6 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Kuzgut.



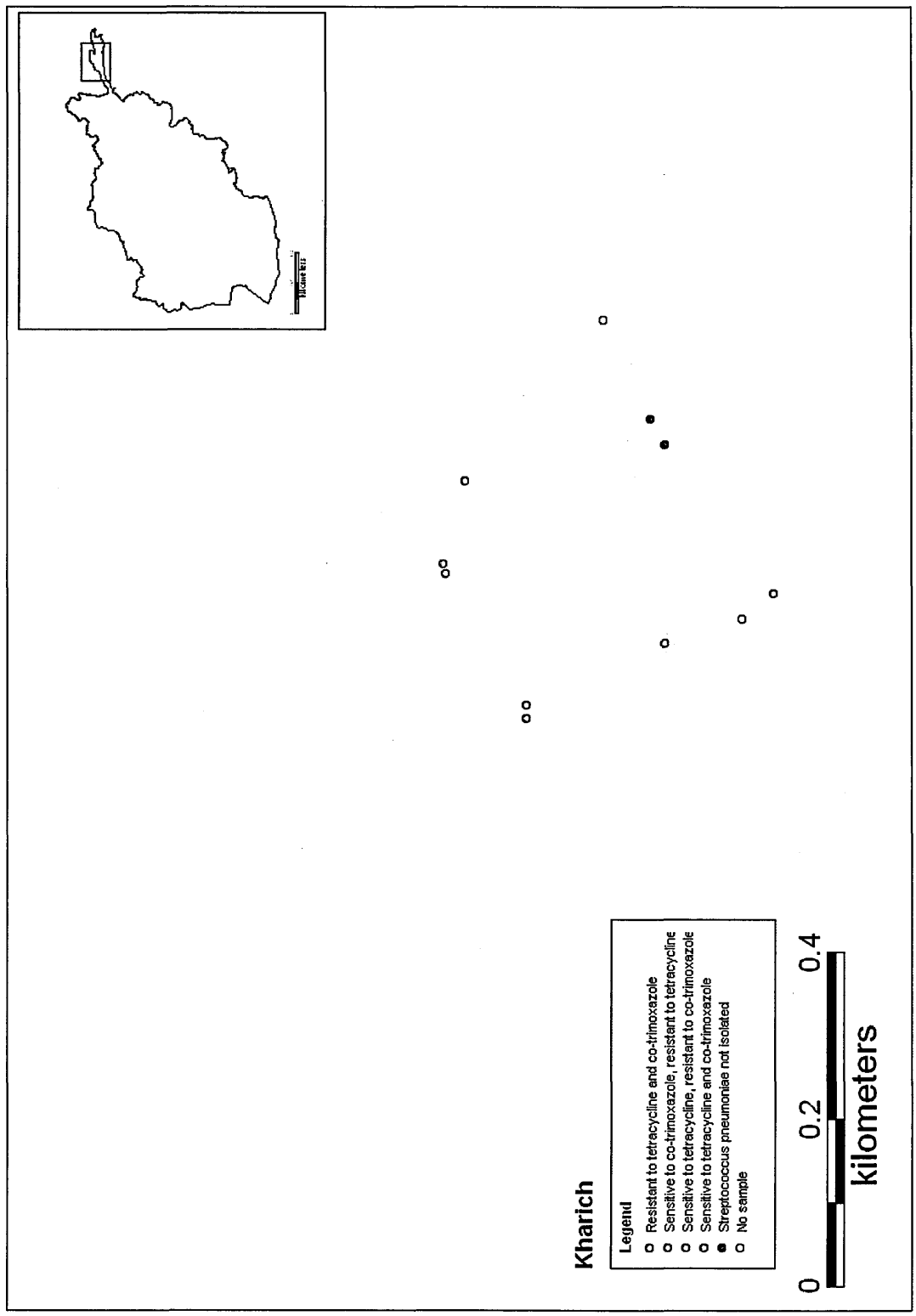
Map 3.7 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Babtangi.



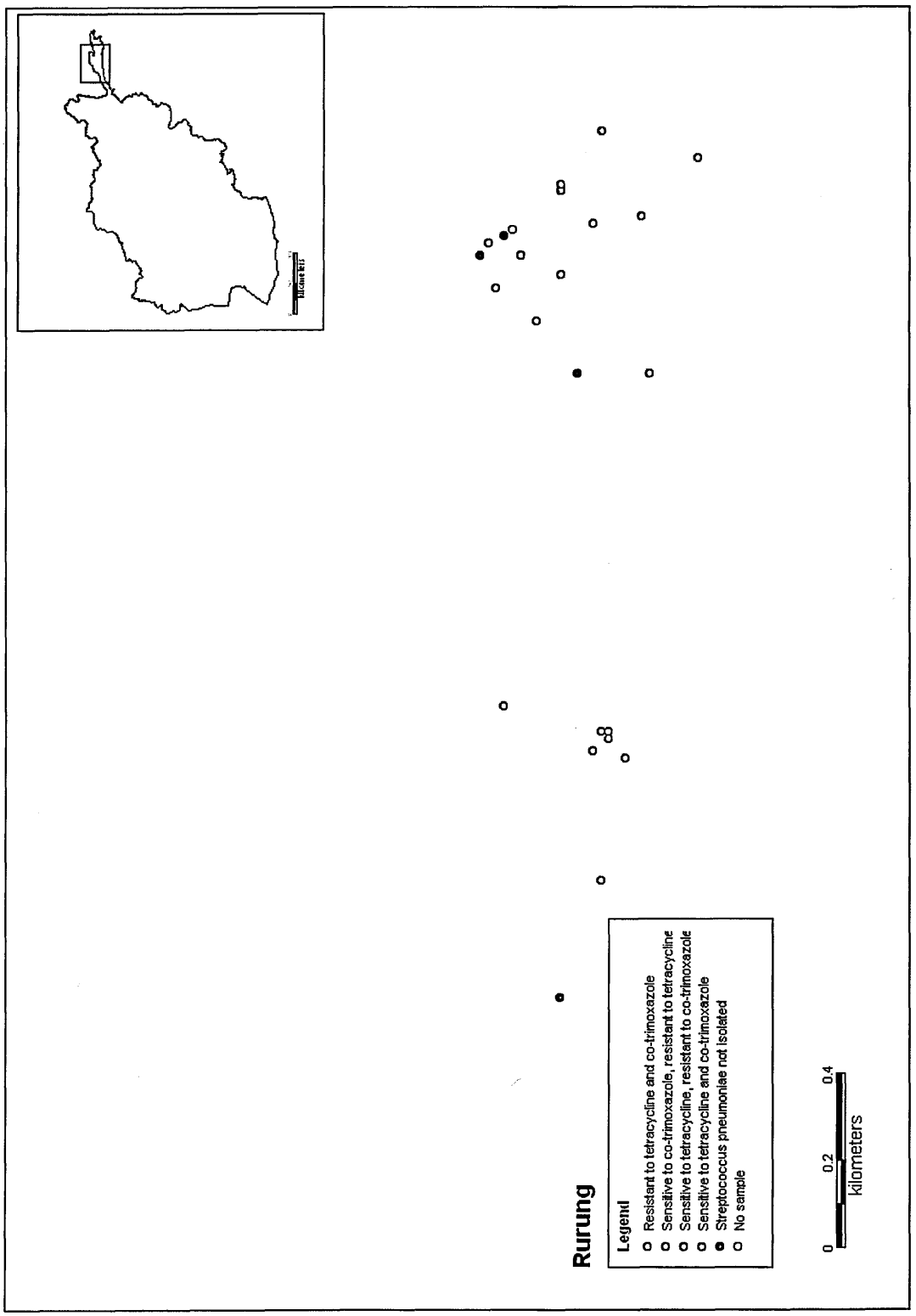
Map 3.8 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Kurut.



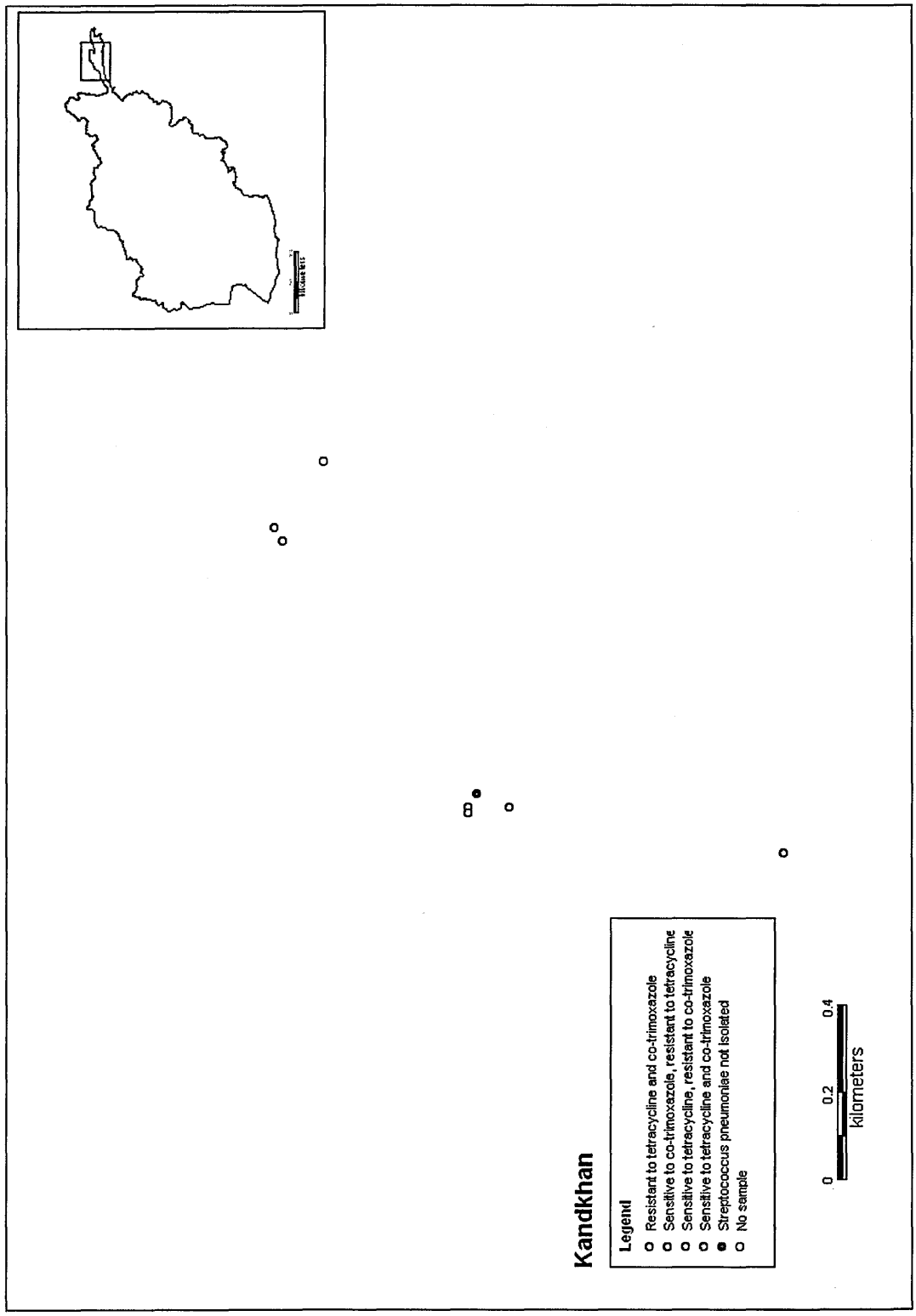
Map 3.9 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Kharich.



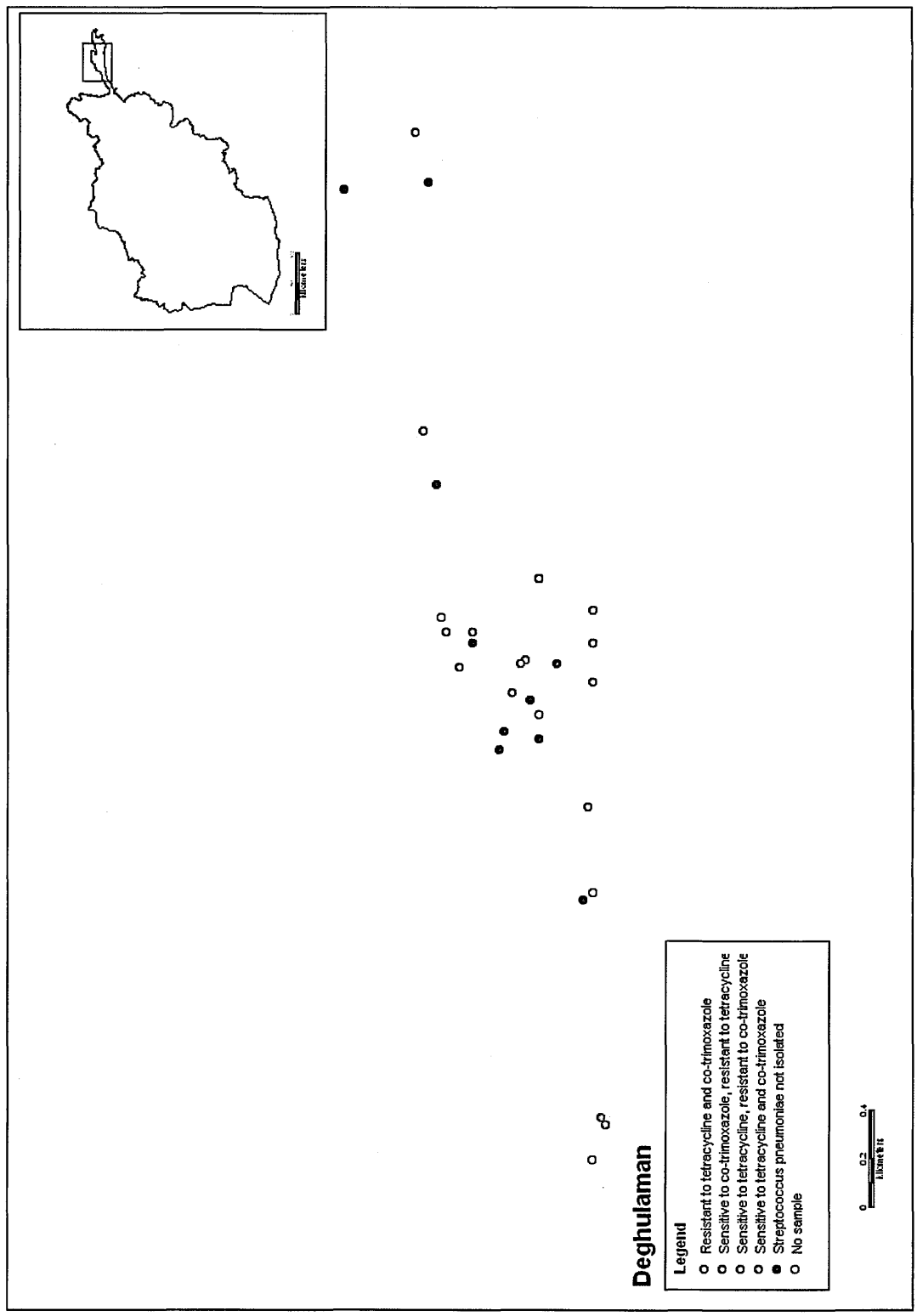
Map 3.10 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Rurung.



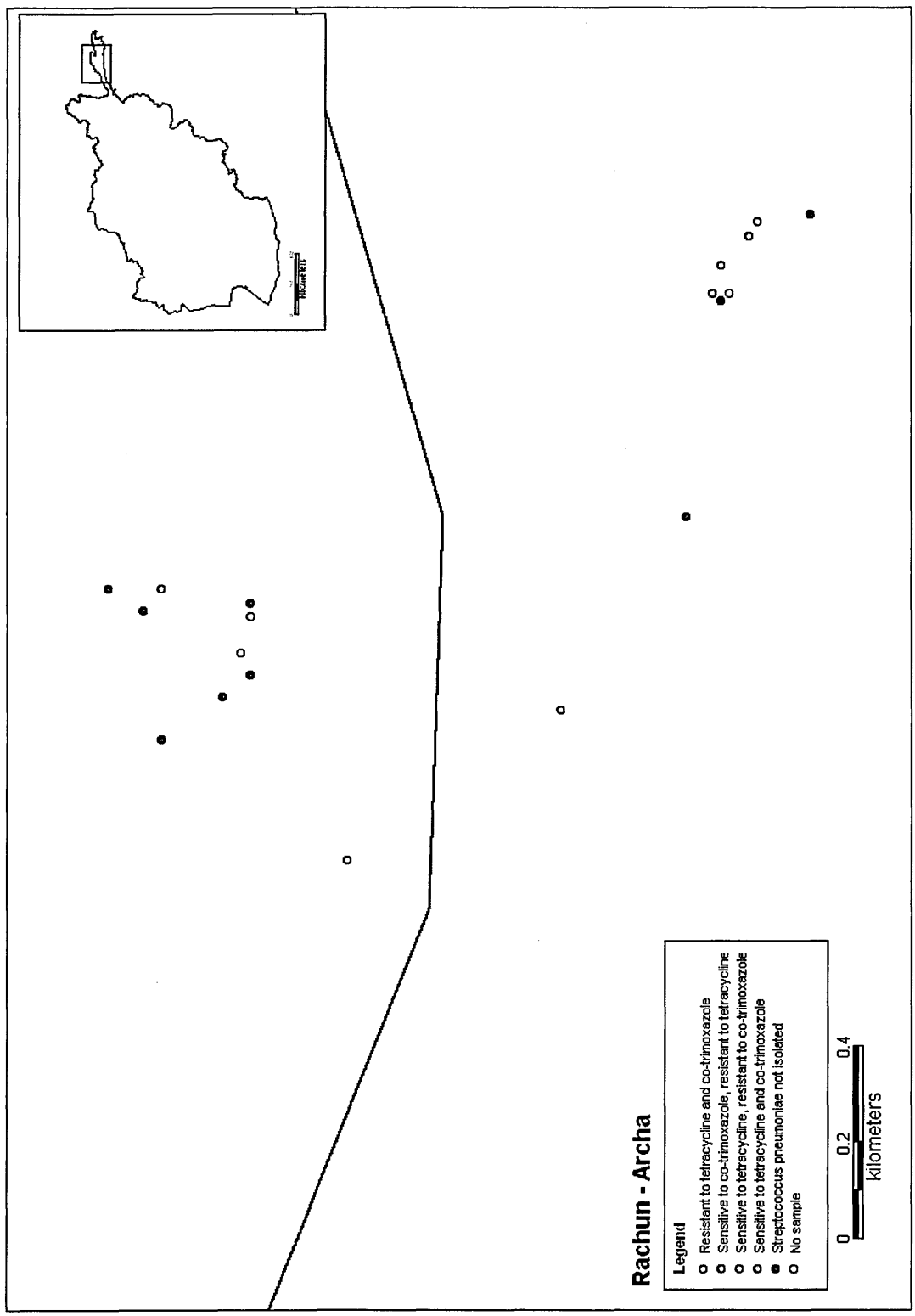
Map 3.11 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Kandkhan.



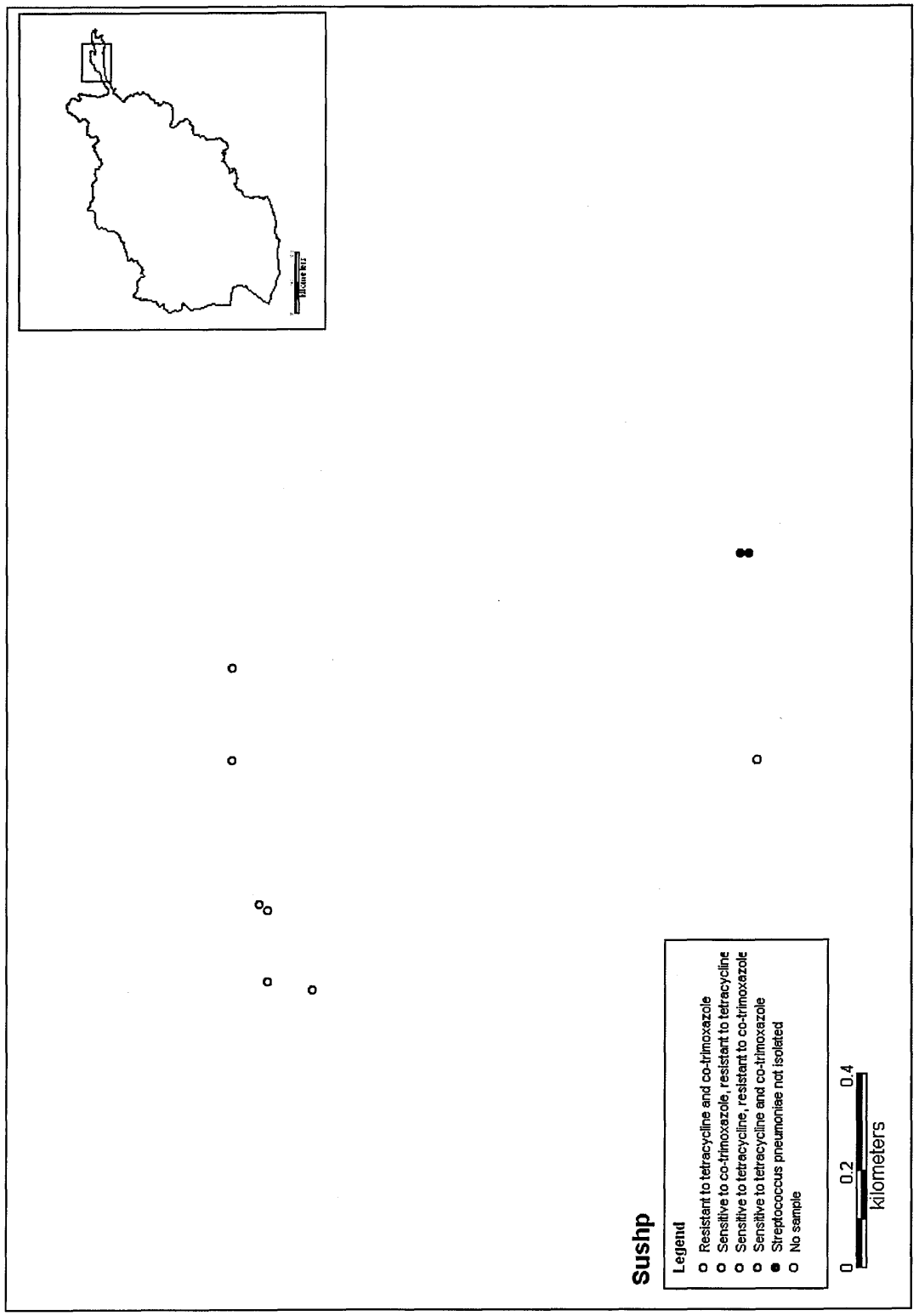
Map 3.12 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Deghulaman.



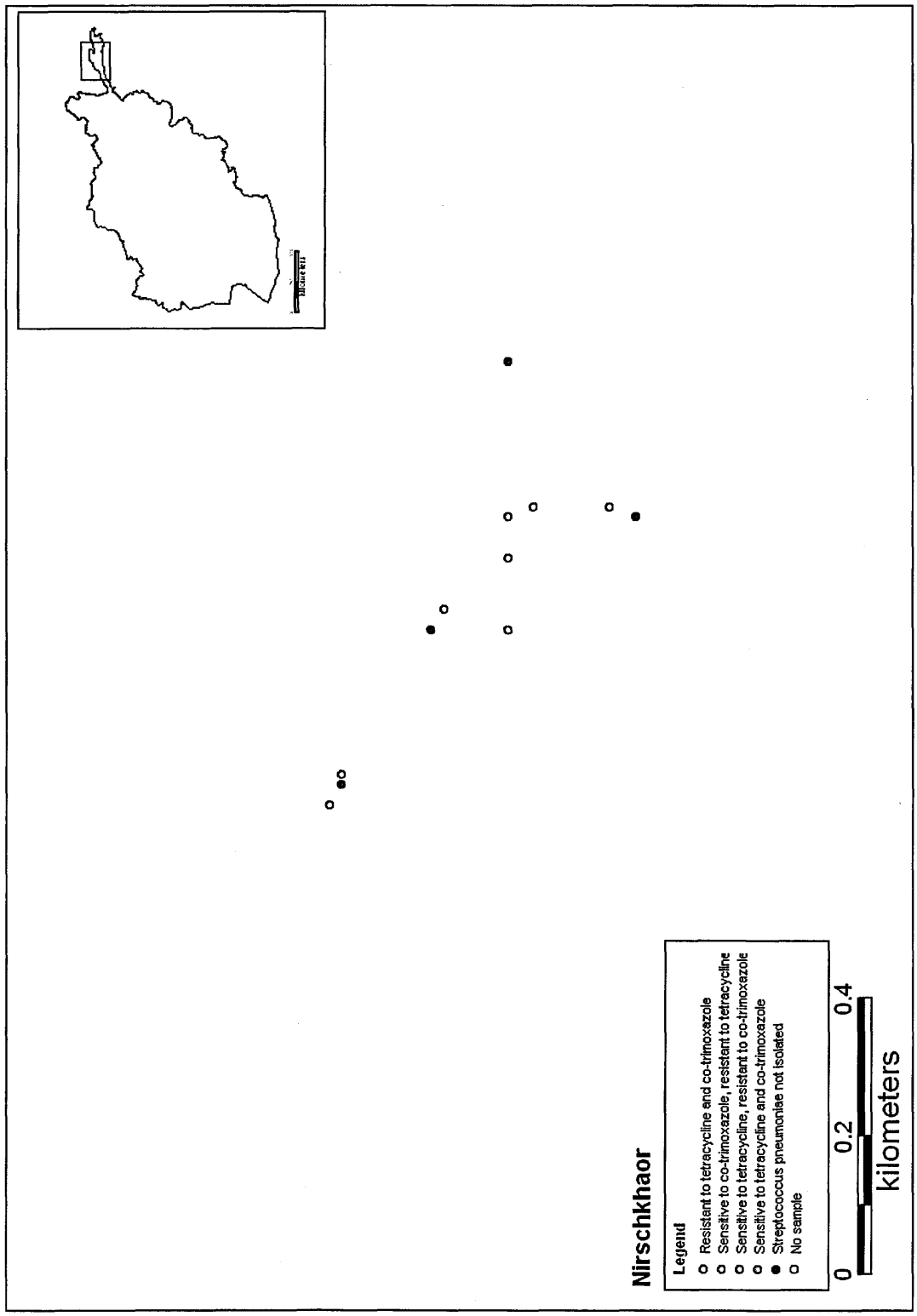
Map 3.13 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Rachun and Archa.



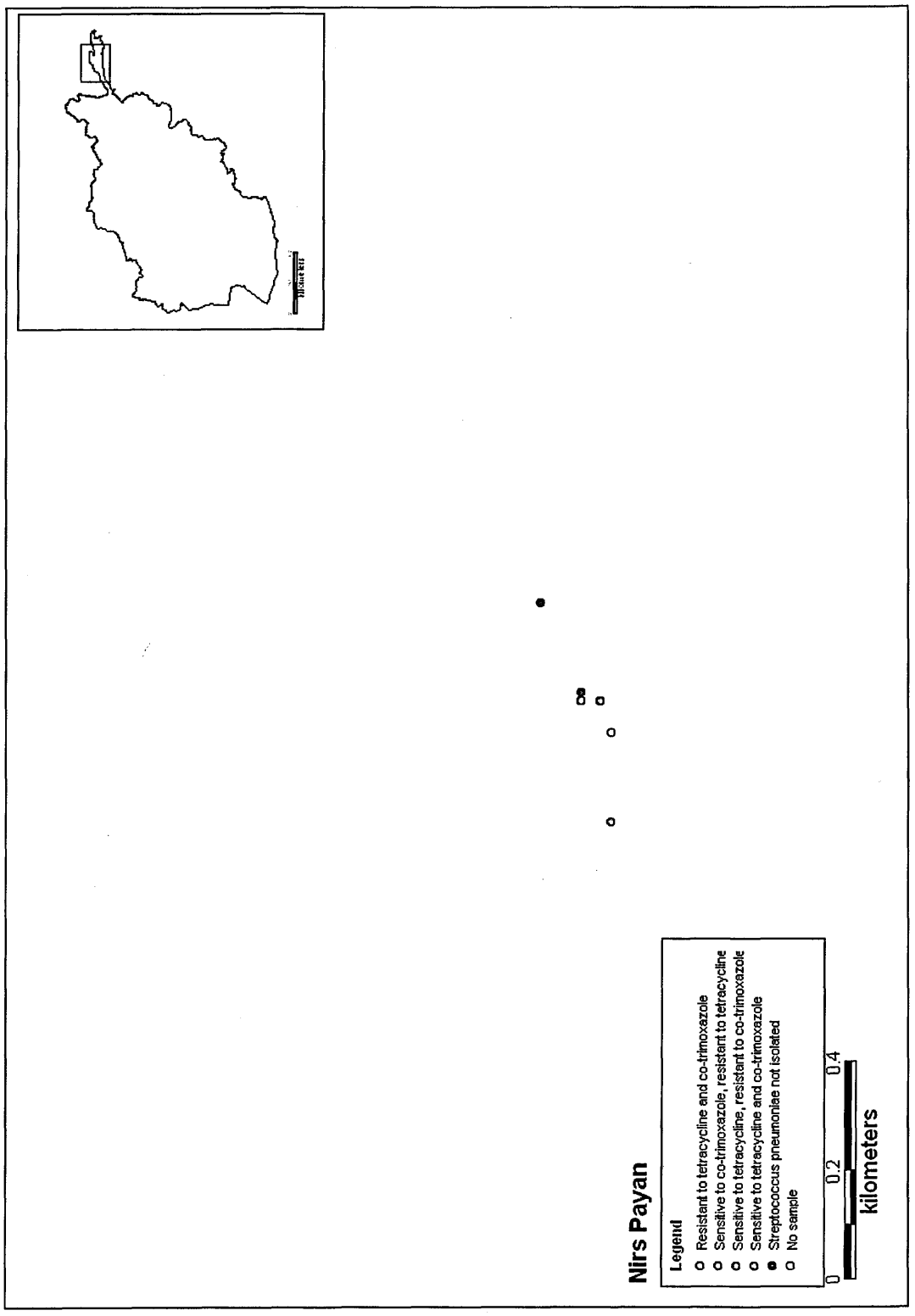
Map 3.14 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Sushp.



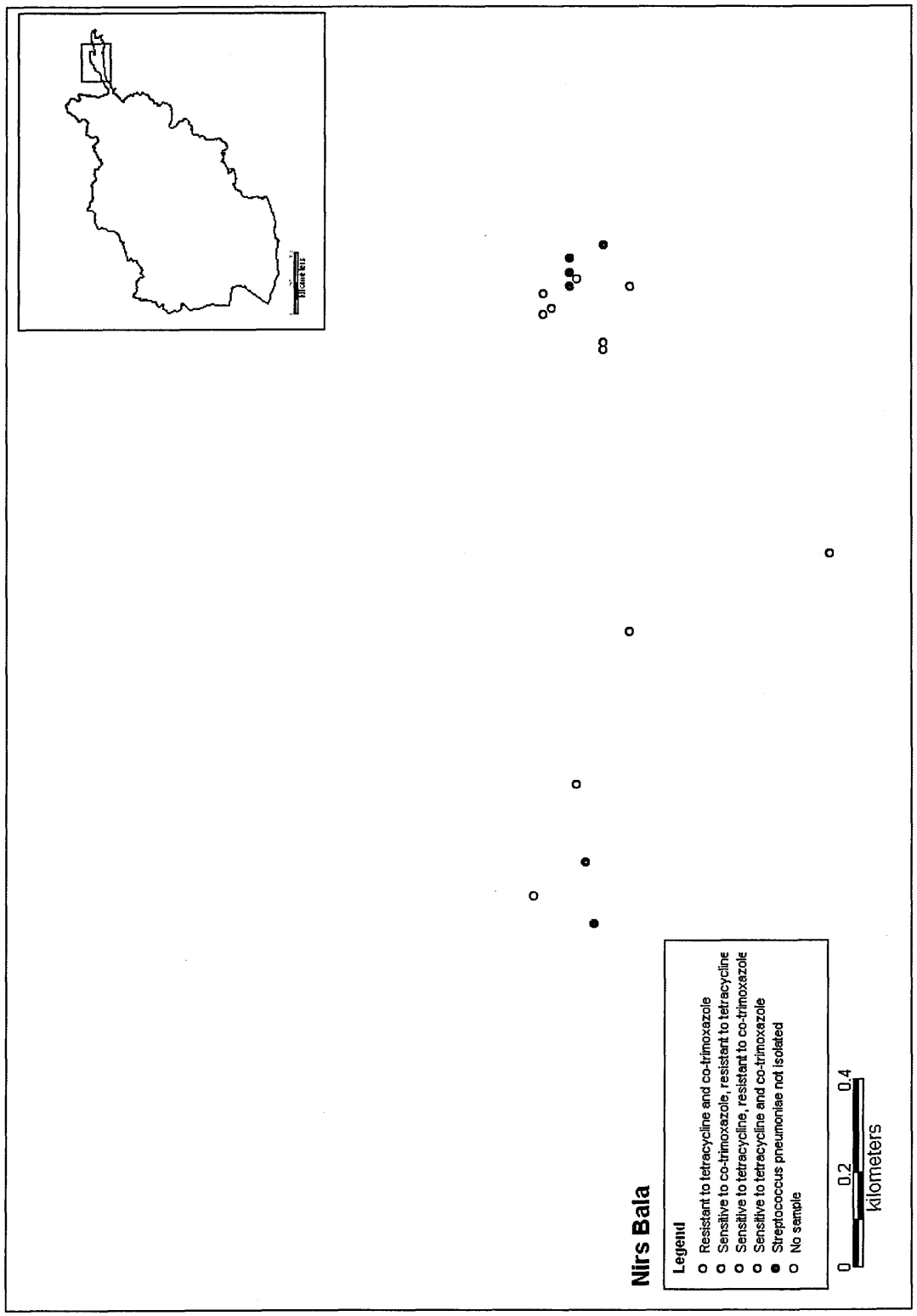
Map 3.15 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Nirschkhaor.



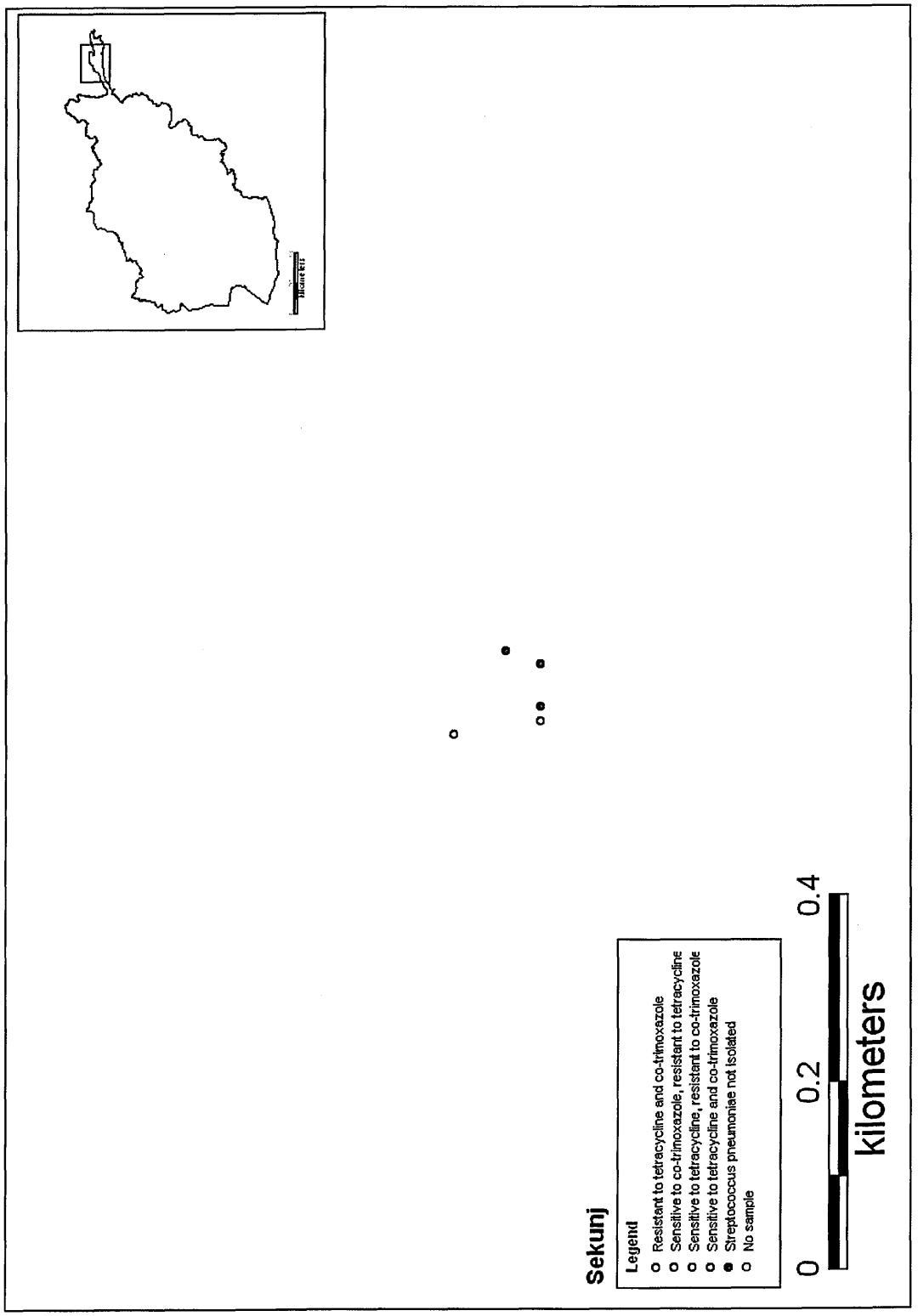
Map 3.16 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Nirs Payan.



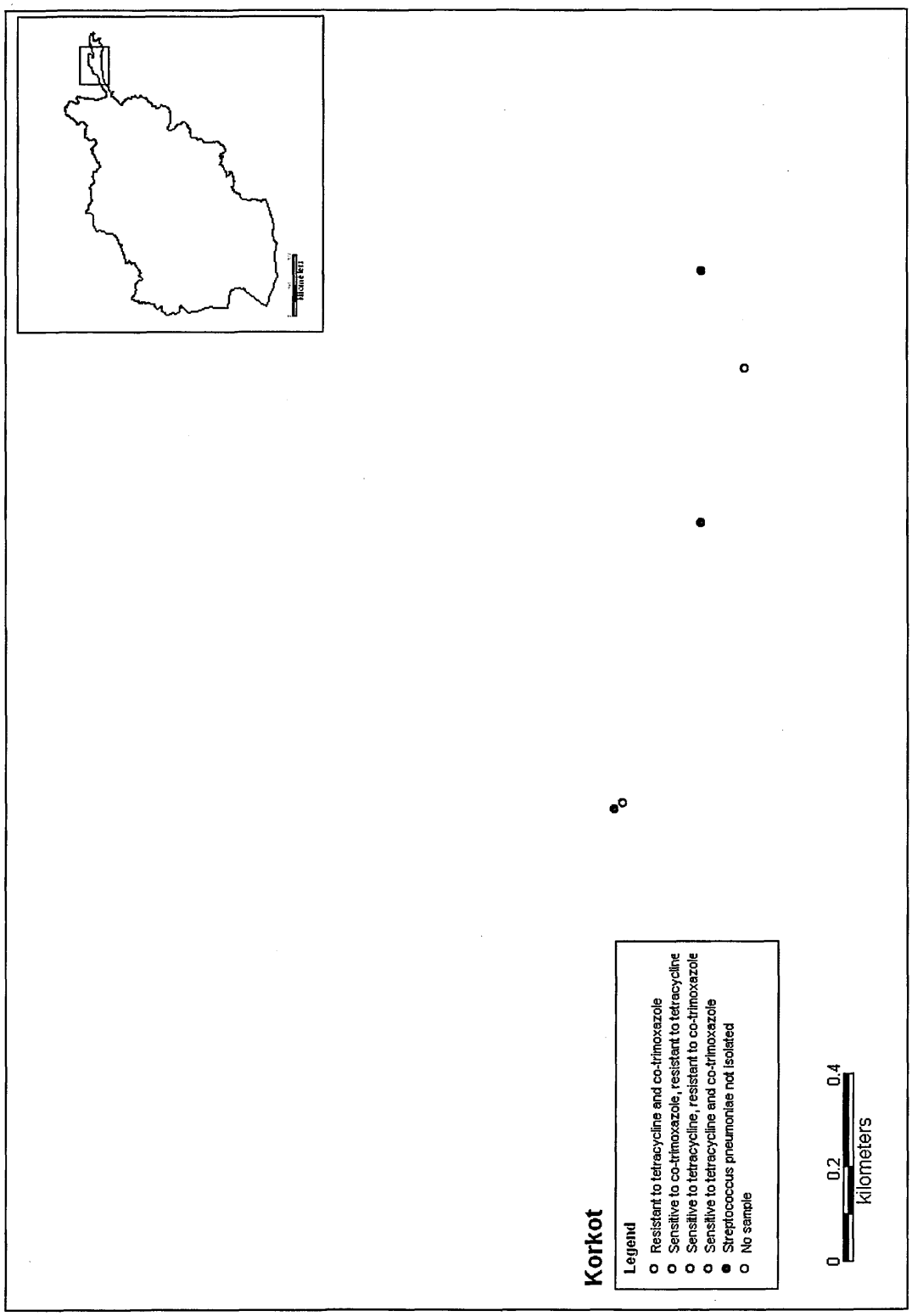
Map 3.17 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Nirs Bala.



Map 3.18 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Sekunj.



Map 3.19 Distribution of households sampled, and antibiotic susceptibility in *Streptococcus pneumoniae* isolated in Korkot.



3.3.6 Sending of isolates of *Streptococcus pneumoniae* to UK and their survival

16 isolates were sent to the UK on Dorset Egg transport medium in April 2008. 12 of these were viable on arrival. One was identified as *Streptococcus mitis*. Unfortunately, the transport container accrued a considerable amount of condensation in transit, and the labels on only six of these isolates were legible, one of which was the *Streptococcus mitis*.

3.3.7 Confirmation of results obtained in Wakhan

Disc sensitivities on the five isolates confirmed the results found in Wakhan, except for one; in the UK, this isolate had a zone of 38mm around the tetracycline disc, whereas in Wakhan there was growth up to the edge of the disc.

3.3.8 Serotyping of isolates

Table 3.24 shows the serotypes of the isolates of *Streptococcus pneumonia* sent back to the UK.

sample	serotype
1	35B
2	35B
3	19F
4	7B
5	18C
6	19F
7	10F
8	18C
9	2
10	7B
11	19F

Table 3.24 Serotypes of isolates of *Streptococcus pneumoniae* sent back to UK

3.3.9 Molecular studies

Table 3.25 shows serotype, multi-locus sequence type (MLST) data and antibiotic susceptibility for isolates sent from Wakhan to the UK.

sample number	serotype	sequence type	aroE	gdh_	gki_	recP	spi_	xpt_	ddl_	eBURST gp	Resistance pattern
1	35B	373	7	13	4	5	7	88	9	singleton	SXT/TET/ERY
2	35B	373	7	13	4	5	7	88	9	singleton	SXT/TET
3	19F	4194	2	5	9	10	17	1	31	45	SXT
4	7B	New 1	7	8	8	6	6	2	8	(337 in gp1)	SXT
5	18C	1381	10	11	4	16	15	1	145	90	SXT
6	19F	4194	2	5	9	10	17	1	31	45	SXT/TET
7	10F	New 2	2	8	62	3	6	88	309	(3735 + 4084 in gp 185)	SXT/TET
8	18C	1381	10	11	4	16	15	1	145	90	SXT/TET
9	2	1794	10	16	54	1	15	1	31	132	SXT/TET
10	7B	New 1	7	8	8	6	6	2	8	(337 in gp1)	SXT/TET
11	19F	New 1	7	8	8	6	6	2	8	(337 in gp1)	SXT/TET

SXT = resistant to co-trimoxazole.

TET = resistant to tetracycline.

ERY = resistant to erythromycin.

Table 3.25 Serotype, MLST and antibiotic susceptibility data for isolates of *Streptococcus pneumoniae* sent from Wakhan to the UK

Table 3.26 shows locations of MLST sequence type entries on the MLST database of known sequence types, and close locus variants of new sequence types.

sample number	serotype	sequence type	entry from MLST database
1	35B	373	373 found in Norway 2000 - 35
2	35B	373	373 found in Norway 2000 - 35
3	19F	4194	4194 found in Burkina Faso 2001 - 19F
4	7B	New 1	SLV of 337 found in Norway 1998 - 19F
5	18C	1381	1381 found in Scotland 2004 - 18C
6	19F	4194	419a found in Burkina Faso 2001 - 19F
7	10F	New 2	DLV of 3735 found in UK - 10A; DLV of 4084 found in UK
8	18C	1381	1381 found in Scotland 2004 - 18C
9	2	1794	1794 found in USA - 17F and 6B; found in Niger - 20
10	7B	New 1	SLV of 337 found in Norway 1998 - 19F
11	19F	New 1	SLV of 337 found in Norway 1998 - 19F

Table 3.26 Locations of MLST sequence type entries on the MLST data base of known sequence types, and close locus variants of new sequence types.

Multi-locus sequence typing (MLST) revealed that four of the 11 isolates were of a sequence type not recorded on the MLST database (held at Imperial College, London). Of these, three (samples 4,10 and 11) were of the same type (here called New 1), all a single locus variant of 337. The fourth (sample 7, here called New 2) was a double locus variant of both 3735 and 4084. The 'New 1' samples contained two (samples 4 and 10) of serotype 7B and one (sample 11) was serotype 19F.

Sample 9 was sequence type 1794, but was a different serotype to previously recorded type 1794 samples.

3.3.10 Discussion of microbiology results

3.3.10.1 Quality control issues

As discussed in section 3.3.2, quality control can be difficult in such a remote area. At all times, CLSI 2005 guidelines and Standard Operating Procedures were followed. The inability to grow the reference strain of *Streptococcus pneumoniae* in the 2006-7 season was highly frustrating, and could, of course, invalidate all the results from that period. The results from the period in 2008, however, in which the reference strain grew well, showed that the techniques employed in the Kipkut laboratory were of an appropriate standard. The results over the two periods were comparable, so there is no reason to suspect that the results in the 2006-7 period were dubious in any way. The only unexplained difference is the significantly higher rate of resistance to oxacillin in the first period. This is discussed in section 3.4.4 on p 177 below.

3.3.10.2 Results are comparable with other similar situations

There are numerous published studies of carriage and antibiotic resistance in *Streptococcus pneumoniae,* which are comparable with the results obtained in Wakhan.

Table 3.26 shows a summary of 22 studies, compiled by the author. (The bracketed numbers refer to the studies listed at the end of the 6 tables in this section)

location	setting	no. children	age range (m)	isolation rate	% res PEN	% res SXT	% res ERY	% res TET
Fiji (9)	not stated	440	3 – 13	44	11	20		
Central African Republic (21)	ill children hospital outpatient	371	?	73	9	6		
Taiwan (3)	community, urban	2905	2 – 84	21	71			
Eastern Europe (5)	hosp outpatient & day care centre	954	0 – 60	27	40			
Botswana (19)	hospital inpatient and outpatient	187	2 – 60	69	2	20		1
Botswana (19)	hospital inpatient and outpatient	62	2 – 60	85	4	23		1
Hong Kong (1)	community, urban	1978	2 – 72	19	58		77	
Belgium (4)	community, urban	467	3 – 36	21	14		61	48
Taiwan (2)	well baby clinic	478	1 – 14	20	90			
India (16)	community, urban and rural	2400	60 – 120	53	3	82		
Vietnam (10)	community, urban and rural	911	12 – 184	44	51	42	50	71
Bangladesh (12)	community, urban and rural	2839	0 – 60	47	7	77	2	
South Africa (8)	clinic	303	1 – 60	40	45		38	
Indonesia (14)	community, urban and rural	484	0 – 25	48	0			
Uganda (18)	community, urban	191	0 – 48	62	83	83	0	29
Zambia (20)	outpatient at hospital	260	1 – 60	72	14	13		
Kazakhstan, (17) Uzbekistan, Kirghizstan	mixed, urban/rural, comm/hosp	630	2 – 59	59	24			
Australia (6)	community, urban	1267	6 – 54	29	1	11		
Mexico (7)	community, urban	450	1 – 60	29	16	42		
USA (11)	rural	200	12 – 60	44	11	44	26	98
Uganda (18)	hospital well child clinic	191	0 – 48	62	84	84	0	29
Canada (12)	community, urban	1322	0 – 60	44	17	38	13	
Malawi	not stated	200	0 – 60	48	22			
mean				***46***	***29***	***42***	***30***	***40***
current study, Afghanistan	**community, rural**	**441**	**0 – 110**	**49**	**17**	**70**	**9**	**40**

Table 3.26 Summary of 22 studies of antibiotic susceptibilty of *Streptococcus pneumoniae.*

Table 3.27 shows isolation rate of *Streptococcus pneumoniae* on nasopharyngeal swabs in 22 studies

location	setting	no. children	age range (m)	isolation rate %
Hong Kong (1)	community, urban	1978	2 – 72	19
Taiwan (2)	well baby clinic	478	1 – 14	20
Taiwan (3)	community, urban	2905	2 – 84	21
Belgium (4)	community, urban	467	3 – 36	21
Eastern Europe (5)	hosp outpatient & day care centre	954	0 – 60	27
Australia (6)	community, urban	1267	6 – 54	29
Mexico (7)	community, urban	450	1 – 60	29
South Africa (8)	clinic	303	1 – 60	40
Fiji (9)	not stated	440	3 – 13	44
Vietnam (10)	community, urban and rural	911	12 – 184	44
USA (11)	rural	200	12 – 60	44
Canada (12)	community, urban	1322	0 – 60	44
mean				***46***
Bangladesh (13)	community, urban and rural	2839	0 – 60	47
Indonesia (14)	community, urban and rural	484	0 – 25	48
Malawi (15)	not stated	200	0 – 60	48
current study, Afghanistan	**community, rural**	**441**	**2 – 110**	**49**
India (16)	community, urban and rural	2400	60 – 120	53
Kazakhstan, Uzbekistan, Kirghizstan (17)	mixed, urban/rural, comm/ hosp	630	2 – 59	59
Uganda (18)	community, urban	191	0 – 48	62
Botswana (19)	hospital well child clinic	187	2 – 60	69
Zambia (20)	hospital inpatient and outpatient	260	1 – 60	72
Central African Republic (21)	outpatient at hospital	371	not stated	73
Botswana (19)	ill children hospital outpatient	62	2 – 60	85

Table 3.27 isolation rate of *Streptococcus pneumoniae* on nasopharyngeal swabs

Comparing the current study with other studies shows the isolation rate to be above the mean. If the lower isolation rate found among the samples transported to Kabul is excluded, the isolation rate for the Wakhan samples is 55%, 9% above the mean.

Table 3.28 highlights the occurrence of resistance to co-trimoxazole.

location	setting	no. children	age range (m)	% res SXT
Central African Republic (21)	ill children hospital outpatient	371	?	6
Australia (6)	community, urban	1267	6 – 54	11
Zambia (20)	outpatient in hospital	260	1 – 60	13
Fiji (9)	not stated	440	3 – 13	20
Botswana (19)	hospital inpatient and outpatient	187	2 – 60	20
Botswana (19)	hospital inpatient and outpatient	62	2 – 60	23
Canada (12)	community, urban	1322	0 – 60	38
Mexico (7)	community, urban	450	1 – 60	42
Vietnam (10)	community, urban and rural	911	12 – 184	42
mean				***42***
USA (11)	rural	200	12 – 60	44
current study, Afghanistan	**community, rural**	**441**	**2 – 110**	**70**
Bangladesh (47)	community, urban and rural	2839	0 – 60	77
India (16)	community, urban and rural	2400	60 – 120	82
Uganda (18)	community, urban	191	0 – 48	83

Table 3.28 Rates of resistance to co-trimoxazole in *Streptococcus pneumoniae* in 13 studies, compared with isolates from Wakhan

Table 3.29 highlights the occurrence of resistance to penicillin.

location	setting	no. children	age range (m)	% res OX
Indonesia (14)	community, urban and rural	484	0 – 25	0
Australia (6)	community, urban	1267	6 – 54	1
Botswana (19)	hospital inpatient and outpatient	187	2 – 60	2
India (16)	community, urban and rural	2400	60 – 120	3
Botswana (19)	hospital inpatient and outpatient	62	2 – 60	4
Bangladesh (13)	community, urban and rural	2839	0 – 60	7
Central African Republic (21)	ill children hospital outpatient	371	?	9
Fiji (9)	not stated	440	3 – 13	11
USA (11)	rural	200	12 – 60	11
Belgium (4)	community, urban	467	3 – 36	14
Zambia 20)	outpatient in hospital	260	1 – 60	14
Mexico (7)	community, urban	450	1 – 60	16
current study, Afghanistan	**community, rural**	**441**	**2 – 110**	**17**
Canada (12)	community, urban	1322	0 – 60	17
Malawi (15)	not stated	200	0 – 60	22
Kazakhstan, Uzbekistan, Kirghizstan (17)	mixed, urban/rural, comm/ hosp	630	2 – 59	24
mean				***29***
Eastern Europe (5)	hosp outpatient & day care centre	954	0 – 60	40
South Africa (8)	clinic	303	1 – 60	45
Vietnam (10)	community, urban and rural	911	12 – 184	51
Hong Kong (1)	community, urban	1978	2 – 72	58
Taiwan (3)	community, urban	2905	2 – 84	71
Uganda (18)	community, urban	191	0 – 48	83
Taiwan (2)	well baby clinic	478	1 – 14	90

Table 3.29 Rates of resistance to penicillin in *Streptococcus pneumoniae* in 22 studies, compared with isolates from Wakhan.

Table 3.30 highlights the occurrence of resistance to erythromycin.

location	setting	no. children	age range (m)	% res ERY
Uganda (18)	community, urban	191	0 – 48	0
Bangladesh (13)	community, urban and rural	2839	0 – 60	2
current study, Afghanistan	**community, rural**	**441**	**2 – 110**	**9**
Canada (12)	community, urban	1322	0 – 60	13
USA (11)	rural	200	12 – 60	26
mean				***30***
South Africa (8)	clinic	303	1 – 60	38
Vietnam (10)	community, urban and rural	911	12 – 184	50
Belgium (4)	community, urban	467	3 – 36	61
Hong Kong (1)	community, urban	1978	2 – 72	77

Table 3.30 Rates of resistance to erythromycin in *Streptococcus pneumoniae* in 8 studies, compared with isolates from Wakhan.

Table 3.31 highlights the occurrence of resistance to tetracycline.

location	setting	no. children	age range (m)	% res TET
Botswana (19)	hospital inpatient and outpatient	187	2 – 60	1
Botswana (19)	hospital inpatient and outpatient	62	2 – 60	1
Uganda (18)	community, urban	191	0 – 48	29
mean				***39***
current study, Afghanistan	**community, rural**	**441**	**2 – 110**	**40**
Belgium (4)	community, urban	467	3 – 36	48
Vietnam (10)	community, urban and rural	911	12 – 184	71
USA (11)	rural	200	12 – 60	98

Table 3.31 Rates of resistance to tetracycline in *Streptococcus pneumoniae* in 6 studies, compared with isolates from Wakhan

Key to studies included in Tables 3.26- 3.31:

1	Chiu et al (2001)	8	Huebner et al (2000)	15	Yomo et al (1997)
2	Lo et al (2003)	9	Russell et al (2006)	16	Jain et al (2005)
3	Chiou et al (1998)	10	Parry et al (2000)	17	Factor et al (2005)
4	Malfroot et al (2004)	11	Samore et al (2001)	18	Joloba et al (2001)
5	Applebaum et al (1996)	12	Kellner and Ford-Jones (1999)	19	Huebner et al (1998)
6	Hansman and Morris (1988)	13	Saha et al. (2003)	20	Woolfson et al (1997)
7	Miranda-Novales et al (1997)	14	Soewignjo et al (2001)	21	Rowe et al (2000)

Comparing the current study with those listed in Tables 3.26-3.31 shows that the results obtained in Wakhan are broadly in line with results from previous studies; isolation of carriage organisms is above the mean, resistance to penicillin, erythromycin and tetracycline are below the mean, and resistance to co-trimoxazole is above the mean. Since the use of antibiotics other than co-trimoxazole was rare, this is not surprising.

3.3.10.3 Geographical distribution of isolates resistant to co-trimoxazole and tetracycline in 2008.

This is shown in Maps 3.2 - 3.19 above, and was examined to determine whether there was geographical clustering of antibiotic resistance in villages, and whether distance from the house where the community health worker lived was significant. Determination of cluster events involves complex mathematics. The author reviewed the maps with Dr Chris Lane, epidemiologist at the Health Protection Agency, who judged that there was no significant clustering of antibiotic resistance.

3.3.10.4 Significance of in vitro breakpoints in clinical disease.

It is conventional for clinicians to receive notifications from microbiology laboratories concerning the antibiotic sensitivities of organisms isolated in diseased patients in terms of 'sensitive' or 'resistant'. This is used as a guide to the choice of antibiotic; if an

isolated bacterium is described on the laboratory report as 'resistant' to an antibiotic in therapeutic use for that patient, then the clinician will often change the antibiotic used to one to which the bacterium is described as 'sensitive'.

In the laboratory, different isolates of bacteria will have clear zones (zones of inhibition) of differing sizes around blotting paper discs with standard concentrations of the antibiotic under test. The antibiotic diffuses into the sensitivity testing medium in the plate, the concentration diminishing as the distance from the disc increases. The bacterium will grow up to the point at which the concentration in the medium is the same as the minimum inhibitory concentration. The zone of inhibition is clear, and can be easily measured. An organism with a high minimum inhibitory concentration will have a small zone of inhibition. The adjectives 'resistant' and 'sensitive' describe whether the zone sizes around the antibiotic discs are less than, or more than a predetermined size. This threshold zone size is known as the breakpoint.

Determination of breakpoints is the work of expert committees, which try to assess the relationship between tissue concentrations of antibacterial drugs at standard doses, their bactericidal activity at those concentrations, and the in vitro activity which is visible in the laboratory. In a review article about the setting of breakpoints, Ferraro (2001) points out that the breakpoints set may differ greatly from place to place. For example, the breakpoint for cefotaxime activity against *Enterobacteriaceae* in the USA is 8 µg/mL, while in the UK, it is 1 µg/mL. One reason for this, as Philips (2001) points out at the same symposium, is that standard recommended dose of a drug may be different in different places.

Another difficulty in this process is that concentrations of antibacterial drugs in different tissues vary greatly, and tissue concentrations in diseased tissue differ from normal tissue (Siegel et al 1999). These difficulties also have an effect on the determination of

recommended doses of antibacterial drugs; a pre-determined 'desirable' serum concentration of a drug is recommended. However, a given serum concentration of a drug will give very different tissue concentrations in different types of tissue - Siegel et al (1999) point out that the concentration of penicillin in inflamed lung tissue may be ten times the concentration in cerebrospinal fluid for the same serum concentration.

The in vitro breakpoint is usually set for an organism without regard to the tissue from which the organism was isolated (an exception to this is discussed below), and those who set the breakpoint have to relate theoretical clinical efficacy, which the breakpoint represents, to the usually prescribed dose of the medication. For example, when determining whether an isolate of *Streptococcus pneumoniae* will respond to a presumed serum concentration of penicillin obtained with a standard dose of penicillin per kg body weight, the breakpoint has to be set to cover *Streptococcus pneumoniae* from cerebrospinal fluid as well as those from lung washouts or sputum. The actual bacteriocidal concentration of the penicillin is the same, but since the penetration of penicillin into the cerebrospinal fluid is less than into other tissues, for a given ***serum*** concentration, a bacterium isolated from the cerebrospinal fluid will have to have a lower minimum inhibitory concentration to penicillin to be killed, than an isolate from the lung tissue if the treatment is to be effective.

For example, a prescribed dose of penicillin may give a serum concentration of 10µg/ml (Siegel - op cit). This will give a concentration in the cerebrospinal fluid of 2µg/ml. If the *Streptococcus pneumoniae* isolate being examined came from cerebrospinal fluid, the antibiotic will only be predicted to be effective at this dose if the minimum inhibitory concentration for the isolate is under 2µg/ml.

However, a serum concentration of 10µg/ml gives a concentration in lung tissue of 20µg/ml. Thus penicillin given at the standard dose will be effective against an isolate

from the lung with a minimum inhibitory concentration of 20µg/ml, which is 10 times higher than an isolate from the cerebrospinal fluid.

Thus treatment with the antibiotic will still be effective for an isolate from the lung with a smaller clear zone size than an isolate from the cerebro-spinal fluid.

The breakpoint for an organism is set for the minimum inhibitory concentration required to be effective in all tissue types. In the above example, the breakpoint is set at $\mathscr{X}$mm, rather than 0.5$\mathscr{X}$. An isolate that gives a zone size of 0.7$\mathscr{X}$mm around the disc will therefore be labelled as being 'clinically effective'. This situation could be described in simplistic terms as 'treatment being clinically effective, despite the bacterium demonstrating in-vitro resistance'.

Given this, it might seem reasonable to set two or more breakpoints for a single organism, depending on the tissue from which it was isolated. Phillips (2001) points to the fact that in some places this has been done for *E coli;* the breakpoint for organisms isolated from the urine is higher (i.e. the zone size is smaller) for some antibiotics, as they are concentrated in the urine. Phillips however, suggests that this may be dangerous, as the clinical information given with a sample may not be accurate, and if, for example, the organism in the urine spreads to the blood to cause septicaemia, clinicians may be under the impression that the antibiotic regime prescribed for the organism isolated from the urine is adequate for the systemic infection.

The bactericidal capacity of co-trimoxazole is likely to be related to the 'area under the curve' of tissue concentration over time. Despite extensive searching and correspondence, it has not been possible to obtain accurate data about the exact relationship of serum concentrations of sulphamethoxazole and trimethoprim, their

synergistic relationship and the relationship between serum concentrations and bactericidal activity.

Reeves and Wilkinson (1979) gave a comprehensive account of the pharmacokinetics and tissue penetration of trimethoprim/sulphonamide combinations. They found that the concentration of trimethoprim in sputum and bronchial secretions was twice that of serum concentrations at steady state in adult subjects. There is no data available for these measurements in children.

The literature concerning the pharmacokinetics of co-trimoxazole in children is very limited. The most comprehensive study is from Zar et al (2006), who looked at 15 children between 11 and 40 months who were HIV positive, but not acutely ill at the time of the study. Their purpose was to determine whether oral co-trimoxazole could be used in place of parenteral co-trimoxazole in the treatment of *Pneumocystis jiroveci* pneumonia, a common infection in people with HIV infection, and a cardinal sign of AIDS. The study looked at serum trimethoprim levels after varying doses of oral co-trimoxazole.

The mean weight of a 12 month-old child in Wakhan is 7.98kg. If this child is given the prescribed dose of co-trimoxazole, which is one tablet of 400mg sulphamethoxazole with 80mg trimethoprim twice a day, this is the equivalent of 10mg per kg of trimethoprim. Zar et al found that a loading dose of 10 mg per kg gave a peak level of 2 µg/ml of trimethoprim at 3 hours in serum.

If the tissue concentrations in children are approximately the same as they are in adults, this would give an approximate peak concentration of trimethoprim of 4µg/ml in the bronchial secretions.

The minimum inhibitory concentration data from the Wakhan isolates of *Streptococcus pneumoniae* (Chart 3.17) shows that 16 out of 86 isolates tested (18.6%) had a minimum inhibitory concentration of above 4µg/ml of trimethoprim. This is in contrast with 81% of isolates which produced a zone of less than 19mm on the sensitivity testing plate.

The E-test strip used contained trimethoprim only, since no E-test for co-trimoxazole is available.

From 2004 to 2008, approximately 135 000 co-trimoxazole tablets were distributed in Wakhan. This is enough for 2 courses of co-trimoxazole per year for every child under five years. 20 children died from acute respiratory infection in that time. The health workers trained in the Wakhan programme did not keep records of those to whom they gave co-trimoxazole, as all but one were functionally illiterate. However, even if the health workers over-prescribed by a large margin, if the true 'resistance' rate were 81%, more than 20 deaths might be expected.

As discussed above, the data available suggests that the set breakpoint is inappropriate in determining whether an isolate would be likely to respond to co-trimoxazole in an acute respiratory infection or not. It may also be appropriate to use a susceptibility testing disc with a higher concentration of co-trimoxazole than the current standard co-trimoxazole disc currently in use (trimethoprim/sulphmethoxazole 1:19, 25µg), since greater accuracy of zone size for organisms with higher minimum inhibitory concentrations would be obtained.

Rasmussen at al (1994) found that in a geographically similar area in Pakistan, 91% of children with acute respiratory infection were successfully treated with oral co-trimoxazole. These children were diagnosed and treated by local women trained as

health volunteers, using a very similar algorithm to that used in Wakhan. 59% of the organisms (either *Streptococcus pneumoniae* or *Haemophilus influenzae)* isolated from the nasopharynx of the sick children, on which sensitivity testing was carried out exhibited 'in vitro resistance' to co-trimoxazole, and 10% 'intermediate susceptibility'; the susceptibilities for individual organisms were not differentiated. There was no difference in treatment outcomes between those from whom a 'resistant' *Streptococcus pneumoniae* was isolated, and those from whom a 'sensitive' organism was isolated. Unfortunately, the primary data for this study was stolen from the researcher's car, and the sizes of zones of inhibition of bacterial growth are not available for analysis of organisms isolated from children whose clinical treatment failed.

There are are two possible interpretations of Rasmussen's data.

The first is that the diagnostic algorithm is not sensitive enough, and that the breakpoint is a true reflection of the effectiveness of co-trimoxazole in treating pneumonia in children. If this were the case, the treatment for the 9% of children whose treatment failed (29 out of 341) failed only because the bacterium was resistant to co-trimoxazole, and that those 29 represented all of the resistant organisms. If 69% of the organisms isolated showed reistance, then those 29 cases represent 69% of all those with a true bacterial pneumonia caused by *Streptococcus pneumoniae* or *Haemophilus influenzae.* Thus the total number with a true pneumonia caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* would be 44, or 13% of the total number of cases, diagnosed by the algorithm; the algorithm had a positive predictive value of 13%.

However, such a low positive predictive value in diagnosis would make the IMCI protocols a very blunt instrument. The evidence put forward by WHO for the selection of the respiratory rates at more than 50 breaths per minute for children 2-11 months,

and 40 breaths per minute for children 12-59 months was based on a review of five studies comparing respiratory rate with 'gold standard' diagnosis by chest X-ray. The review found the lowest positive predictive value to be 69% (WHO 1991).

The other interpretation is that the algorithm is effective, but the breakpoint is inappropriate. In this situation, the large majority of the 341 cases had a true bacterial pneumonia caused by *Streptococcus pneumoniae* or *Haemophilus influenzae*. If the specificity of the algorithm is 80% (the mean of the specificities in the WHO review, 1991), the 273 of the 341 cases could be assumed to have a true pneumonia. If 9% of these fail to respond to treatment due to the causative organism being resistant to co-trimoxazole, then 248 of these cases are caused by a bacterium that is clinically responsive to co-trimoxazole. This is 73% of the total, showing that a maximum of 27% of the bacteria are 'resistant'. The breakpoint would have to be altered to reflect this. With the current breakpoint, 69% of the isolates are 'resistant' or of intermediate susceptibility; the breakpoint would have to be reset at a higher minimum inhibitory concentration to exclude 60% of those currently included as 'resistant'.

This is obviously an over-simplification of the situation. A bacterial pneumonia could be caused by a bacterium other than *Streptococcus pneumoniae* or *Haemophilus influenzae.* Treatment success and failure depend on many factors as well as the level of susceptibility of the disease-causing organism to the antibiotic prescribed.

The true situation is likely to lie between the two scenarios. However, the evidence points towards the possibility that the current breakpoint is not appropriate for the clinical situation of assessing the therapeutic effectiveness of co-trimoxazole in childhood pneumonia. More research is required into the nature of the in vitro breakpoint for co-trimoxazole, and the relationship of the breakpoints to clinical situations.

Following the argument of Philips (2001) above, there could be a case for setting a large margin of safety as *Streptococcus pneumoniae* causing pneumonia in a child could cause a bacteraemia and then a meningitis. If this were to happen, then having set the breakpoint to cover an appropriate minimum inhibitory concentration in the cerebro-spinal fluid (i.e. much higher for co-trimoxazole, or, more likely, a different choice of antibiotic) could save lives. This strategy, however, would mean significant changes in national antibiotic policies, with large cost implications. A course of amoxicillin for a two year-old child costs about $0.55 as a syrup or about $0.35 as tablets, whereas co-trimoxazole costs $0.09.

Straus et al (1998) compared treatment of severe and non-severe pneumonia (as defined by WHO guidelines in IMCI) with co-trimoxazole and amoxycillin in 577 children in Pakistan, and found that there was no difference in the outcomes for the two medicines in non-severe pneumonia, but that there were more treatment failures in the co-trimoxazole group in children with severe pneumonia (66/203 for co-trimoxazole vs 18/99 for amoxycillin). *Streptococcus pneumoniae* was isolated from 48 blood culture specimens, of which 35 were in the co-trimoxazole treatment group. Of this 35, 12 were sensitive to co-trimoxazole (MIC <1/19µg/l trimethoprim/sulfamethoxazole), 8 were of intermediate sensitivity (1/19-2/38) and 15 were resistant (>2/38). Whether the bacterium was sensitive, of intermediate sensitivity or resistant made no difference to the rate of treatment failure in either severe or non-severe pneumonia. These findings could call into question the usefulness of breakpoints in any context of predicting clinical outcomes. However, the number of isolates was very small (there were only six isolates of *Streptococcus pneumoniae* in the 'treatment failures in the severe pneumonia' group), so drawing firm conclusions from these data is not possible.

3.3.10.5 Sample transportation

Given the fragility of *Streptococcus pneumoniae* and the length, nature and difficulty of the journey from Wakhan to the UK, Dorset Egg medium has been shown to be effective for this purpose.

The condensation issue causing labelling confusion was very frustrating, and underlines the importance of secure marking.

3.3.10.6 Vaccination policies

There are four vaccines against *Streptococcus pneumoniae* in current use.

- *Pneumovax* vaccine is a capsular polysaccharide vaccine was first licenced in 1979. The first type had activity against 14 capsular serotypes (described as 14 valent). In 1989 a new *Pneumovax* was released which was 23 valent. It is used only in adults.
- *Prevnar*, a heptavalent vaccine was licenced in 2000.
- *Prevnar 13*, containing six additional serotypes, was licenced in 2009. It is a protein conjugate vaccine.
- *Synflorix* is a decavalent protein conjugate vaccine, first licenced in 2008.

Both Prevnar and Synflorix are licenced for use in children.

Table 3.32 shows the coverage of these vaccines, compared to the isolates from Wakhan. Isolates not covered by the protein conjugate vaccines are highlighted in red

Serotype	Pneumovax	Synflorix	Prevnar 7	Prevnar 13	Wakhan
1	x	x		x	
2	x				**1**
3	x			x	
4	x	x	x	x	
5	x	x		x	
6A				x	
6B	x	x	x	x	
7B					**2**
7F	x	x		x	
8	x				
9N	x				
9V	x	x	x	x	
10A	x				
10F					**1**
11A	x				
12F	x				
14	x	x	x	x	
15B	x				
17F	x				
18C			x	x	2
19F	x	x	x	x	2
19A	x			x	1
20	x				
22F	x				
23F	x	x	x	x	
33F	x				
35B					**2**

Table 3.32 Serotypes of *Streptococcus pneumoniae* contained in four commercial vaccines, compared with isolates sent back to the UK from Wakhan.

Six of the eleven serotypes present in the isolates sent from Wakhan are not covered by the protein conjugate vaccines shown in Table 3.32, and only one of these six is covered by the polysaccharide vaccine. Since these are carriage organisms rather than disease-causing organisms, the significance of this is unclear. However, given these data, further research into the distribution of serotypes causing disease is required.

3.3.10.7 Multi-locus sequence typing

The multi-locus sequence typing of the strains sent from Wakhan shows two novel strains. The relative geographical isolation of Wakhan may contribute to less exchange of strains from other areas of Afghanistan, although there are no other strains from Afghanistan currently on the multi-locus sequence typing database.

3.4 General Discussion

3.4.1 Quality control

Small laboratory facilities in remote areas reduce the need to transport fastidious organisms to bigger laboratory facilities in urban areas. Transportation reduces the isolation rate of these organisms, and also reduces the local impact of the work. If such facilities are operated by single individuals, the work could be of poor quality, due to lack of peer monitoring, and thus give misleading results. Quality control is vital for all antibiotic susceptibility work. The experience of this programme was that quality control was adequate, and that a laboratory facility can be successfully operated in such conditions.

3.4.2 Isolation rates

There was no difference between isolation rates in males and females, and also no age gradient. Many previous studies have found that the isolation rate of *Streptococcus pneumoniae* from nasopharyngeal samples falls as children get older. Anecdotal evidence suggests that starting school may be associated with reduced isolation rates. Children in Wakhan do not start school until seven years of age, and even then, attendance is not 100%, especially amongst girls. It is possible that if more nasopharyngeal samples had been collected from children over seven, a gradient would have been seen.

3.4.3 Antibiotic resistance

Resistance to oxacillin was higher in samples isolated in 2006-7 than in samples isolated in 2008. The supply of penicillins was not observed to be higher in the earlier period than in the later. It is possible that a resistant strain had emerged before 2006. This may have been due to the supply of penicillins from traders being used with inadequate doses, and for inadequate courses, both of which would promote

resistance. As the antibiotic supply from the ORA project became reliable, the use of penicillins from other sources reduced, thus exerting little selection pressure in favour of a strain resistant, which then disappeared.

No change in susceptibility was seen for co-trimoxazole, tetracycline or erythromycin.

High levels of in vitro reistance to co-trimoxazole were found. Section 3.3.10.4 on p173 above discusses the setting of in vitro breakpoints for antibiotic disc sensitivity. Implementation of the Wakhan Community Health Programme saved around 50 young children's lives between 2005 and 2008. There did not seem to be a significant level of treatment failure in acute respiratory infection, although this could not be formally quantified. The use of antibiotics by women with very limited training can be justified by these results.

40% of isolates were resistant to tetracycline. In the project, systemic tetracyclines were only used on a very few occasions for three men with suspected Brucellosis. Tetracycline was widely used in eye ointment form. However, tetracyclines seemed to be very popular with traders to sell to the population, possibly because it came as a very brightly coloured yellow and red capsule, and these were widely recognised as 'strong medicine' by people in Wakhan. Full-dosage courses were very rarely adhered to with these capsules.

There did not appear to be any clustering of resistance to co-trimoxazole or tetracycline, and no effect of distance from the health worker's house.

3.4.4 Serotyping and molecular studies on isolates of *Streptococcus pneumoniae*

Streptococcus pneumoniae is a fragile organism, and transportation of isolates is difficult. The survival rate of isolates transported to the UK was 75%. Dorset Egg medium is an effective medium for this, but it would be better if such studies could be done as close to the area of collection as possible. The advantage would have been that a much greater proportion of the isolates could have been serotyped. This would have been very useful in examining the potential effectiveness of vaccination with the currently available commercial vaccines, as six of the 11 isolates which were serotyped are not included in the vaccines. However, cost is an important factor in this, in that purchasing a kit for serotyping would have cost in excess of £1200. To purchase such a kit for 219 isolates would have been prohibitively expensive, especially since guaranteeing the 'cold chain' in transporting the kit from the UK to Wakhan would not have been possible.

Multi-locus sequence typing of the 11 isolates sent to the UK showed a diversity of types, and revealed two novel strains. The geographical distribution of these novel strains needs to be established by further research in Wakhan and surrounding areas.

4 Final Discussion and Conclusion

4.1 Ethical issues

Introduction of antibiotics

It would obviously have been much better to have started nasopharyngeal sampling and antibiotic susceptibility testing of *Streptococcus pneumoniae* before starting the health worker training and introducing antibiotics to the community. Anecdotally, antibiotic supply before 2002 was limited to what was brought into the community by traders, and it would have been ideal to compare susceptibility before and after the introduction of antibiotics. However, funding for setting up a laboratory was not available before mid-2004. The evidence of the effectiveness of the IMCI algorithm for case management of children with acute respiratory illness was very strong, and it would therefore have been unethical to delay the introduction of a programme known to be effective in preventing child death in order to collect 'pre-antibiotic' samples. However, an attempt at some data collection was made. Contact was made with the Aga Khan University Department of Microbiology in Karachi, Pakistan; permission was obtained from the AKU Ethics committee to collect samples, and approximately 130 oropharyngeal swabs were collected in November 2003 from children aged one and two. These were frozen in a brine/ice mixture at -16 ° centigrade, and sent to the AKU, and stored at -70° Centigrade. Unfortunately, by the time funding was available to analyse these, the samples had been discarded.

Consent

Informed consent is a difficult issue in communities where literacy levels are low.

In Wakhi culture, the head of the household is the figure from whom consent should be sought, and usually parents would consult with them before giving permission. Hence an adult man in his 40s would often ask his very elderly father or uncle for permission.

Wakhan is a 'communal' culture, rather than an 'individualistic' culture. In various areas of life, communal registers for each household were used, for example, when distributing fertiliser, or government census data collection. Since most people are illiterate, the use of an individual consent form in Dari, which would then be translated orally into Wakhi, seemed inappropriate, since the legal status of a form would be lost unless the Wakhi translation could be verified, which was impossible.

When the first request for ethical approval was submitted to The Open University, the proposal was to create a register; the register would have the purpose of the research printed in Dari on the front page, and then the household would be entered on the subsequent pages with the names of the subjects and those giving permission. Permission would be indicated by the application of a signature in the case of those who could write their name, or more commonly with the application of a finger-print, which was common practice.

However, when permission for the project was sought from Medical Research Ethics Committee of the Government of the Islamic Republic of Afghanistan, Ministry of Health, the committee insisted on individual consent forms. There were two Americans and a European on the committee of eight, who may have influenced this decision. It was also a consistent observation, when discussing our work with officials from Government institutions in Kabul, that they had very little idea of what life was like outside the cities, let alone in the very remote areas of the country.

A consent form was written in English and translated into Dari. However, it is very difficult to get any official document translated into simple language. No matter how great the necessity for simplicity of language was impressed on the translator, it always ended up in 'high-brow' Dari; the cultural concept was that, if it were not high brow, it was not properly official. Although the translation went through several revisions, each increasingly simple, the final form was still more 'high-brow' than was desirable, but the translator refused to simplify it further, saying that if it were any simpler, it would not be credible as an official document. Very few of the people of Wakhan are literate, and almost none of them were able to understand the consent form. When it was read to them, very few of them could understand it fully. The meaning of the form was then explained in Wakhi, the local language, and if consent was given, this was indicated by the application of a signature in the case of those who could write their name, or more commonly, the application of a finger print to the form by those who could not.

Image 4.1 Informed consent was indicated with a finger print on the consent form.

Many times, once the helper started to explain the content of the form, the head of household would say "oh, don't worry to go through all that; it's fine, it's fine." In that situation, the author would insist that the meaning of the form was explained nonetheless.

Given all the constraints on this process, the author is confident that no swabs were taken against the wishes of the family of the participants, and that they were as informed as possible about the purposes and methods of the study.

The text of the consent form, and an example form in Dari are attached in Appendices 3 and 4.

4.2 Overall impact of the project

For generations, the population of Wakhan have been a marginalised ethnic minority, most years managing to coax just enough from the very poor mountain soil to survive. They have had no access to any government services, except the maintenance of border security, and have suffered very high mortality rates. The ORA Community Health Programme sought, and even now in 2011 continues to seek, to bring some relief to these very poor people. This thesis has shown that, with the co-operation of the community, a small outside agency can help to reduce child mortality by implementing versions of well-attested international health protocols, appropriately adapted to local circumstances by people who have tried hard to understand the culture and practices of a specific population.

In the developed world, the medical community rightly agonizes over the inappropriate use of antibiotics, which promotes resistance, which may in time, it is feared, lead to antibiotics becoming useless. Many health professionals have questioned the author about whether it is wise to put antibiotics into the hands of health workers with so little

training. However, the implementation of the Wakhan Community Health programme, including the *sina baghal* protocol, saved at least 50 children from death between 2004 and 2008, the antibiotic component probably having a significant role in this. Cynics could say that these children may well then die of something else a short time later; this may be so in some cases, but by implementing an integrated development programme with maternal and child health, family 'spacing', nutrition and agricultural components and indoor smoke reduction, it was hoped to reduce such a risk.

The author set up the microbiology surveillance project to see if reduced antibiotic susceptibility was becoming a problem. As is common in such circumstances, the research has thrown up more questions than it has answered; it is unclear whether the use of co-trimoxazole by mainly illiterate female health workers with very limited training is leading to a clinically significant reduction in the susceptibility of *Streptococcus pneumoniae.* The setting of an appropriate in vitro breakpoint is of great importance in this, but given the constraints involved in setting breakpoints, it is unclear how this can be done.

It would be ideal if nasopharyngeal sampling of *Streptococcus pneumoniae* were to continue in Wakhan on a regular basis. Despite the laboratory facility being available, this is not currently possible. The author returned to the UK for the foreseeable future in July 2008, as his children needed to go to school, and the ex-patriate team who are continuing the health programme have no interest in the microbiological aspect of the project, nor the skills to continue it. To run the programme, it took a great deal of determination and even bloody-mindedness, and the current ex-patriate team have other community development priorities in their sights. The level of education of local people in the project area was so low that it was not possible to train a local person to continue the microbiology surveillance. This is regrettable, but given the situation in Afghanistan, and the overwhelming development need, it is not surprising.

It is hoped that the publication of the findings of this research will encourage others to consider similar work in other areas of the world, both in terms of community health intervention and microbiological surveillance. If nothing else, this author's experience demonstrates that, although very difficult, these programmes are possible, even in very challenging areas, and can yield beneficial results. As the very first line of this thesis stated, in 2008, 8.8 million children died before the age of five, and 60% or more of these might have been prevented by currently available interventions. Programmes like this one in Wakhan are needed in many communities around the world.

If all the support, supervision and supply to the female health workers in Wakhan were to disappear, what they learned about feeding young children, nursing sick children and hygienic delivery would stay with them. These skills require no materials, only knowledge, and would continue to have a significant impact on child health in the community.

Finally, and most of all, the author's greatest joy is that he and his family were able to bring a sense of hope to a community which had little, showing that change and progress is possible with concerted effort, even in the face of considerable challenges, and demonstrating that someone from outside their community cared about them, and whether their children lived or died.

4.3 Final Conclusion

The data presented in this thesis show that implementation of a primary health care programme focusing on a few health issues, delivered mainly by women with little schooling and limited community healthcare training, is associated with a reduction in child mortality in a remote rural area of Afghanistan. The implementation of an

adaptation of the Integrated Management of Childhood Illness algorithm for managing acute respiratory illness with co-trimoxazole, providing health education particularly on nutrition, provision of supplementary feeding and improving vaccination coverage, was associated with a reduction mortality for children up to two years of age.

The data show that a system of antibiotic susceptibility surveillance can be established in such a remote location if adequate logistical support and supply can be maintained. It has also been shown that although *Streptococcus pneumoniae* is a fragile organism, samples can be sent from remote locations to a reference laboratory using Dorset Egg medium, if some simple appropriate measures are taken.

Two novel strains of *Streptococcus pneumoniae* were collected from nasopharyngeal sampling in children in the area of Afghanistan studied, and they have been added to the international database of strains of *Streptococcus pneumoniae,* differentiated by multi-locus sequence typing.

Six out of 11 isolates of *Streptococcus pneumoniae* sent to the reference laboratory were of serotypes not covered by the protein conjugate vaccines commercially available for prevention of disease in children. This may have consequences for the effectiveness of a vaccination programme. The composition of the vaccine may need to be reconsidered.

The data show that the implementation of a community-based primary health care programme as described does raise concerns about the emergence of *Streptococcus pneumoniae* with resistance to co-trimoxazole in vitro. 9% of isolates had intermediate sensitivity and 70% were resistant to co-trimoxazole, the antibiotic used in the Wakhan programme, using the standard CLSI breakpoints. However, examination of the published literature suggests that the breakpoints used may not be appropriate for this

setting. More research is needed into the nature of in vitro breakpoints, and the relationship of the breakpoints to clinical situations.

Bibliography

Albrich, W., Monnet, D., Harbarth, S., Antibiotic Selection Pressure and Resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes. Emerging Infectious Diseases* 10 (3), 514-7, 2004

Appelbaum, C., Gladkova, C., Hryniewicz, W., Kojouharov, B., Kotulova, D., Mihalcu, F., Schindler, J., Setchanova, L., Semina, N., Trupl, J., Tyski, S., Urbaskova, P., Jacobs R., Carriage of Antibiotic-Resistant *Streptococcus pneumoniae* by Children in Eastern and Central Europe: A Multicenter Study with Use of Standardized Methods, *Clinical Infectious Diseases,* 23 (4), 712-717, 1996

Arason V., Kristinsson, K., Sigurdsson, J., Stefansdottir, G., Molstad, M., Gudmundsson, S., Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study, *BMJ* 313, 387-391, 1996

Ashworth, A., Shrimpton, R., Jamil, K., Growth monitoring and promotion: review of evidence of impact, *Maternal & Child Nutrition,* 4 (supp1), 86 - 117, 2008

Bang, A., Bang, R., Baitule, S., Reddy, M., Deshmukh, M., Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India, *Lancet* 354, 1955–61, 1999

Bedos, J-P., Chevret, S., Chastang, C., Geslin, P., Regnier, B., Epidemiological features of and risk factors for infection by *Streptococcus pneumoniae* strains with diminished susceptibility to penicillin: findings of a French survey. *Clin Infect Dis* 22, 63–72, 1996

Bruce N., Rogelio Perez-Padilla, R., Albalak, R., Indoor air pollution in developing countries: a major environmental and public health challenge, *Bulletin of the World Health Organization,* 78 (9), 1078-92, 2000

Bryce, J., Boschi-Pinto, C., Shibuya, K., Black, R. and the WHO Child Health Epidemiology Reference Group, WHO estimates of the causes of death in children, *Lancet,* 365, 1147–52, 2005

Caulfield, L., Huffman, S., Piwoz, E., Interventions to improve intake of complementary foods by infants 6 to 12 months of age in developing countries: Impact on growth and on the prevalence of malnutrition and potential contribution to child survival, *Food and Nutrition Bulletin,* 20 (2), 83-200, 1999

Chan, M., Return to Alma-Ata,*Lancet,* 372, 865 - 866, 2008

Chiou, C., Liu, Y., Huang, T., Hwang, W., Wang, J., Lin, H., Yen, M., Hsieh, K.,: Extremely High Prevalence of Nasopharyngeal Carriage of Penicillin-Resistant *Streptococcus pneumoniae* among Children in Kaohsiung, Taiwan: *Journal of Clinical Microbiology,* 36 (7), 1933-1937, 1998

Chiu, S., Ho, P., Chow, F., Yuen, K., Lau, Y., Nasopharyngeal Carriage of Antimicrobial-Resistant *Streptococcus pneumoniae* among Young Children Attending 79 Kindergartens and Day Care Centers in Hong Kong, *Antimicrobial Agents and Chemotherapy,* 45 (10), 2765–2770, 2001

Clinical and Laboratory Standards Institute, Performance Standards for Antimicrobial Susceptibility Testing; Fifteenth Informational Supplement M100-S15, volume 25 no 1. CLSI, 2005

Crook. D., Brueggemann, A., Sleeman, K., Peto, T., Pneumococcal Carriage, chapter 9 of *The Pneumococcus, (editors Tuomanen, Mitchell, Morrison, Spratt,), American Society for Microbiology Press,* 2004

de Souza A., Peterson K., Cufino E., Gardner J., Craveiro M., Ascherio, A., Relationship between health services, socioeconomic variables and inadequate weight gain among Brazilian children, *Bulletin of the World Health Organization* 77, 895–905, 1999

Edmonston, B., and Andes, N., Community variations in infant and child mortality in Peru, *Journal of Epidemiology and Community Health,* 37, 121-126, 1983

Factor, S., LaClaire, L., Bronsdon, M., Suleymanova, F., Altynbaeva, G., Bakhtiyar, A., Kadirov, B., Shamieva, U., Dowell, S., Schuchat, A., Facklam, R., Schwartz, B., Chorba, T., *Streptococcus pneumoniae* and *Haemophilus influenzae* type b Carriage, Central Asia, *Emerging Infectious Diseases,* 11 (9), 1476-9, Sept 2005

Ferraro, M-J., Should We Reevaluate Antibiotic Breakpoints? *Clinical Infectious Diseases,* 33 (Supp 3), s227-229, 2001

Garner, P., Panpanich, R., Logan, S., Is routine growth monitoring effective? A systematic review of trials, *Arch Dis Child* 82, 197–201, 2000

Garrod, L., The selective bacteriostatic action of Gentian Violet, *BMJ* 2434, p290-1, 1942

Gerein N., and Ross. D., Is growth monitoring worthwhile? An evaluation of its use in three child health programmes in Zaire, *Social Science & Medicine,* 32 (6), 667-675, 1991

Goossens, H., Ferech, M., Vander Stichele, R., Elseviers, M., Outpatient antibiotic use in Europe and association with resistance: a cross-national database study, *Lancet,* 365, 579 - 587, 2005

Gray, B., Converse, G., Dillon H., Epidemiologic studies of *Streptococcus pneumoniae* in infants; acquisition, carriage and infection in the first 24 months of life, *Journal Infectious Disease* 142, 923-33, 1980

Haines, A., Sanders, D., Lehmann, U., Rowe, A., Lawn, J., Jan, S.,. Walker, D., Bhutta , Z., Achieving child survival goals: potential contribution of community health workers: *Lancet,* 369, 2121–31, 2007

Hansman, D., and Morris, S., Pneumococcal Carriage amongst Children in Adelaide, South Australia, *Epidemiology and Infection,* 101 (2), 411-417, 1988

Hopkirk, P., *The Great Game: the Struggle for Empire in Central Asia*, Oxford University Press, 1991

Huebner, R., Wasas, A., Mushi, A., Mazhani, L., Klugman, K. Nasopharyngeal carriage and antimicrobial resistance in isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in children under 5 years of age in Botswana, *Int J Infect Dis* 3, 18-25, 1998

Huebner, R., Wasas, A., Klugman, K., Prevalence of nasopharyngeal antibiotic-resistant pneumococcal carriage in children attending private paediatric practices in Johannesburg, *S Afr Med J.* 90(11),1116-21, 2000

Jain, A., Kumar, P., Awasthi, S. High nasopharyngeal carriage of drug resistant *Streptococcus pneumoniae* and *Haemophilus influenzae* in North Indian schoolchildren, *Tropical Medicine & International Health,* 10 (3), 234-239, 2005

Jaloba, M., Bajaksouzian, S., Palavecino, E., Whalen, C., Jacobs, M., High prevalence of carriage of antibiotic-resistant *Streptococcus pneumoniae* in children in Kampala Uganda, *International Journal of Antimicrobial Agents* 17, 395–400, 2001

Jones, G., Steketee, R., Black, R., Bhutta, Z., Morris, S. and the Bellagio Child Survival Study Group, How many child deaths can we prevent this year? *Lancet,* 362, 65-71, 2003

Kapil, U., & Pradhan, R., Integrated Child Development Services Scheme (ICDS) and its impact on nutritional status of children in India and recent initiatives, *Indian Journal of Public Health,* 43, 21–25, 1999

Karim, F., Huq, N., Brown, L. & Chowdhury, A., Growth monitoring in the context of a primary health care programme, *Food and Nutrition Bulletin* 15, 192–199, 1994

Keay, J., *'Where Men and Mountains Meet: the Explorers of the Western Himalayas, 1820-75'*, John Murray, 1977

Kellner, J., McGeer, A., Cetron, M., Low, D., Butler, J., Matlow, A., Talbot, J., Ford-Jones, E., The use of *Streptococcus pneumoniae* nasopharyngeal isolates from

healthy children to predict features of invasive disease,. *The Pediatric Infectious Disease Journal,* 17(4),279-86, 1998

Kellner, J., and Ford-Jones, L., *Streptococcus pneumoniae* Carriage in Children Attending 59 Canadian Child Care Centers *Arch Pediatr Adolesc Med.* 153,495-502, 1999

Khan, A., Hussain, H., Omer, S., Chaudry, S., Ali, S., Khan, A., Yasin, Z., Khan, I., Mistry, R., Baig, I., White, F., Moulton, L., Halsey, N., High incidence of childhood pneumonia at high altitudes in Pakistan: a longitudinal cohort study, *Bulletin of the World Health Organization* 87,193-199, 2009

Kidane, G., Morrow, R., Teaching mothers to provide home treatment of malaria in Tigray, Ethiopia: a randomised trial, *Lancet,* 356, 550–55, 2000

Kreutzmann, H., Felmy, S., Wakhan Woluswali in Badakhan; observations and refelections from Afghanistan's periphery. *Erdurkunde,* 58 (2), 97-117, 2004

Lankester, T., Setting up Community Health Programmes, 2nd Edition, *Macmillan/ TALC,* 2000

Lehman, D., Gratten, M., Montgomery, J., Susceptibility of pneumococcal carriage to penicillin provides a conservative estimate of susceptibility of invasive pneumococci. *Ped Infect Dis J,* 16, 297–305, 1997

Lewin, S., Dick, J., Pond, P., Zwarenstein, M., Aja, G., van Wyk, B., Bosch-Capblanch, X., Patrick, M., Lay health workers in primary and community health care. *Cochrane Database of Systematic Reviews* Issue 1. Art. No.: CD004015, 2005

Lo, W., Wang, C., Yu, C., Chu, M., Rate of nasopharyngeal carriage, antimicrobial resistance and serotype of *Streptococcus pneumoniae* among children in northern Taiwan, *J Microbiol Immunol Infect,* 36 (3), 175-81, 2003

Malfroot, A., Verhaegen, J., Dubru, J-M., Van Kerschaver, E., Leyman, S., A cross-sectional survey of the prevalence of *Streptococcus pneumoniae* nasopharyngeal carriage in Belgian infants attending day care centres: *Clin Microbiol Infect.* 10(9), 797-803, 2004

Mastro, T., Nomani, N., Ishaq, Z., Ghafoor, A., Shaukat, N., Esko, E., Leinonen, M., Henrichsen, J., Breiman, R., Schwartz, B., Use of nasopharyngeal isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae* from children in Pakistan for surveillance for antimicrobial resistance, *Ped Infect Dis J,* 12 (10), 824-30, 1993

Médecins Sans Frontières, *MSF Clinical Guidelines Diagnostic and Treatment Manual, 4th Edition,* Médecins Sans Frontières, 1999 (http://www.refbooks.msf.org/msf_docs/en/Clinical_Guide/CG_en.pdf)

Miranda Novales M., Solorzano Santos, F., Guiscafre Gallardo, H., Leanos Miranda, B., Echaniz Aviles, G., Carnalla Barajas, M., Palafox Torres, M., Munoz Hernandez, O., *Streptococcus pneumoniae*: low frequency of penicillin resistance and high resistance to trimethoprim-sulfamethoxazole in nasopharyngeal isolates from children in a rural area in Mexico, *Arch Med Res.* 28(4), 559-63, 1997

Parry, C., Diep, T., Wain, J., Hoa, T., Gainsborough, M., Nga, D., Davies, C., Phu, N., Hien, T., White, N., Farrar, J., Nasal Carriage in Vietnamese Children of *Streptococcus*

pneumoniae Resistant to Multiple Antimicrobial Agents, *Antimicrobial Agents and Chemotherapy,* 44 (3), 484–488, 2000

Phillips, I., Maximizing Antimicrobial Efficacy/Minimizing Antimicrobial Resistance: A Paradigm for the New Millennium: Proceedings of a Symposium Held at the American Academy of Arts and Sciences, Cambridge, Massachusetts, 7-8 December 1999, *Clinical Infectious Diseases,* 33, (sup 3), s230-232, 2001

Polo, Marco, Travels of Marco Polo, Book 1 chapter 32 tr Henry Yule, *published in Wikisource, http://en.wikisource.org/wiki/The_Travels_of_Marco_Polo/Book_1/Chapter_32*

Rasmussen, Z., Implications of cotrimoxazole resistance for the treatment of childhood pneumonia, Presented at the *Global Congress on Lung Health, 29th World Conference of IUATLD/UICTMR (Paris), 1995*

Rasmussen, Z., Pio, A., Enarson,P., Case management of childhood pneumonia in developing countries: recent relevant research and current initiatives, *International Journal Tuberculosis and Lung Disease* 4(9),807–826, 2000

Rasmussen, Z., Rahim, M., Shamsuddin, Nomani, N.K., Ahmed, K., Ali, L., Drug Resistance in nasopharyngeal cultures does not predict effectiveness of co-trimoxazole for treatment of childhood pneumonia in Pakistan; a prospective cohort study, *34th Interscience Conference on Antimicrobial Agents and Chemotherapy,* 1994, abstract J129, and unpublished paper

Reeves, D., Wilkinson, P., The pharmacockinetics of trimethoprim and trimethoprim/ sulphonamide combinations, including penetration into body tissues, *Infection 7* (sup 4), s331-340, 1979

Ross, R., Acquired tolerance of pneumococcus to M+B 693, *Lancet, i:1207-1208, 1939*

Rowe, A., Deming, M., Schwartz, B., Wasas, A., Rolka, D., Rolka, H., Ndoyo, J., Klugman, K., Antimicrobial resistance of nasopharyngeal isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae* from children in the Central African Republic, *Pediatr Infect Dis J.* 19 (5), 438-44, 2000

Rudan, I., Boschi-Pinto, C., Biloglav, Z., Mulhollandd, K., Campbelle, H., Epidemiology and etiology of childhood pneumonia, *Bulletin of the World Health Organization,* 86, 408–416, 2008

Russell, F., Carapetis, J., Ketaiwai, S., Kunabul, V., Taoi, M., Biribo, S., Seduadua, A., Mulholland, E., Pneumococcal nasopharyngeal carriage and patterns of penicillin resistance in young children in Fiji, *Ann Trop Paediatr.,* 26(3), 187-97, 2006

Saha, S., Baqui, A., Darmstadt, G., Ruhulamin, M., Hanif, M., El Arifeen, S., Santosham, M., Oishi, K., Nagatake, T., Black, R., Comparison of Antibiotic Resistance and Serotype Composition of Carriage and Invasive Pneumococci among Bangladeshi Children: Implications for Treatment Policy and Vaccine Formulation, *J Clin Microbiol.* 41(12), 5582-7, 2003

Samore, M., Magill, M., Alder, S., Severina, E., Morrison-De Boer, L., Lyon, J., Carroll, K., Leary, J., Stone, M., Bradford, D., Reading, J., Tomasz, A., Sande, M., High rates of

multiple antibiotic resistance in *Streptococcus pneumoniae* from healthy children living in isolated rural communities: association with cephalosporin use and intrafamilial transmission, *Pediatrics* 108(4), 856-65, 2001

Savage-King, F. and Burgess, A., Nutrition for Developing Countries, 2nd edition, *OUP* 1993,

Sazawal, S., Black, R., Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials, *Lancet Infect Dis* 3, 547-56, 2003

Schroeder D., and Brown, K., Nutritional status as a predictor of child survival; summarizing the association and quantifying its global impact, *Bulletin of the World Health Organization,* 72 (4), 569-579, 1994

Shahrani, M. N. The Kirghiz and Wakhi of Afghanistan; Adaptation to Closed Frontiers. *University of Washington Press,* 1979

Siegel, R., The Significance of Serum vs Tissue Levels of Antibiotics in the Treatment of Penicillin-Resistant *Streptococcus pneumoniae* Community-Acquired Pneumonia, *Chest,* 116, 535-538, 1999

Sleeman, K., Daniels, L., Gupta, S., Maiden, M., Miller, E., George, R., Knox, K., Griffiths, D., Peto, T., Moxon, R., Crook, D., *3rd International Symposium Pneumococci and Pneumococal Disease, 2002, Session R-10, abstract no. 14*

Smith, T., Lehman, D, Montgomery, J., Gratten, M., Riley, I., Alpers, M., Acquisition and invasiveness of different serotypes of *Streptococcus pneumoniae* in young children, *Epidemiology and Infection,* 111, 27-39, 1993

Smith, K., Samet, J., Romieu, R., Bruce, N., Indoor air pollution in developing countries and acute lower respiratory infections in children, *Thorax,* 55, 518-532, 2000

Soewignjo, S., Gessner, B., Sutanto, A., Steinhoff, M., Prijanto, M., Nelson, C., Widjaya, A., Arjoso, S., *Streptococcus pneumoniae* nasopharyngeal carriage prevalence, serotype distribution, and resistance patterns among children on Lombok Island, Indonesia, *Clin Infect Dis.,* 32(7), 1039-43, 2001

Straus, W., Qazi, S., Kundi, Z., Nomani, N., Schwartz, B. Antimicrobial resistance and clinical effectiveness of co-trimoxazole versus amoxycillin from pneumonia among children in Pakistan: randomised controlled trial. *Lancet* 352, 270-5, 1998

UNICEF (2007), Revisiting Growth Monitoring and its Evolution to Promoting Growth as a Strategic Program Approach: Building Consensus for Future Program Guidance: Report of a Technical Consultation *UNICEF,* 2007

UNICEF 2009, (1) UNICEF Press Release, September 10th 2009 *http:// www.unicef.org/media/media_51087.html*

UNICEF 2009, (2) State of the World's Children 2009. *UNICEF http://www.unicef.org/ sowc09/docs/SOWC09_U5MR_rankings.pdf*

UNICEF 2009, (3) State of the World's Children 2009. *UNICEF http://www.unicef.org/ sowc09*

United Nations 2009 United Nations, Millenium Goals Report 2009., *http://www.un.org/millenniumgoals/pdf/MDG%20Report%202009%20ENG.pdf*

United Nations Millennium Declaration, Resolution adopted by the General Assembly [without reference to a Main Committee 2000, (A/55/L.2)] 55/2/III.19. *(http://www.un.org/millennium/declaration/ares552e.pdf)*

Ure, J., *Shooting Leave; Spying Out Central Asia in the Great Game,* Constable and Robinson, 2009

Victora, C., Kirkwood, E., Ashworth, A., Black, R., Rogers, S., Sazawal, S., Campbell, H., Gove, A., Potential interventions for the prevention of childhood pneumonia in developing countries: improving nutrition, *American Journal of Clinical Nutrition,* 70(3), 309-320, 1999

von Grebmer, K., Nestorova, B., Quisumbing, A., Fertziger, R., Fritschel, H., Pandya-Lorch, R., Yohannes, Y., *Global Hunger Index. International Food Policy Research Institute,* 2009

Wain, J., Walsh, A., Setting up a research laboratory in Vietnam; the agony and the ecstacy. *PHLS Microbiology Digest* 12 (4), 208-11, 1994

Wardlaw, T., White Johansson, E., Hodge, M., Pneumonia: The forgotten killer of children, *The United Nations Children's Fund (UNICEF)/World Health Organization (WHO),* Geneva, 2006 (http://www.unicef.org/publications/files/Pneumonia_The_Forgotten_Killer_of_Children.pdf)

Werner, D., Sanders, D., Questioning the Solution, *Health Wrights, 1997 http:// (www.healthwrights.org/books/QTSonline.htm)*

WHO 1978, Declaration of Alma-Ata, *International Conference on Primary Health Care, Alma-Ata, USSR, 6-12 September 1978, (http://www.who.int/publications/ almaata_declaration_en.pdf)*

WHO 1989, Strengthening the performance of community health workers in primary health care: report of a WHO study group,. *Geneva: World Health Organization Technical Report Series No 780, 1989.*

WHO 1991, Technical bases for the WHO recommendations on the management of pneumonia in children at first level facilities, *WHO/ARI/91.20 (http://whqlibdoc.who.int/ hq/1991/WHO_ARI_91.20.pdf)*

WHO 2001 (1), WHO Global Strategy for Containment of Antibiotic Resistance, 2001, p1 *(http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf)*

WHO, 2001 (2), "IMCI Model Chapter for Textbooks", *http:////whqlibdoc.who.int/hq/ 2001/WHO_FCH_CAH_01.01.pdf*

WHO 2008 The world health report 2008: primary health care now more than ever, *World Health Organization 2008, ISBN 978 92 4 156373 4 (http://www.who.int/whr/ 2008/whr08_en.pdf)*

Woolfson, A., Huebner, R., Wasas, A., Chola, S., Godfrey-Faussett, P., Klugman, K., Nasopharyngeal carriage of community-acquired, antibiotic-resistant *Streptococcus*

pneumoniae in a Zambian paediatric population, *Bulletin World Health Organization,* 75 (5), 453-62, 1997

World Food Programme, *Emergency Field Operations Pocketbook WFP 2002* (at *http:// www.unicef.org/emerg/files/WFP_manual.pdf)*

Yomo, A., Subramanyam, V., Fudzulani, R., Kamanga, H., Graham, S., Broadhead, R., Carriage of penicillin-resistant pneumococci in Malawian children, *Ann Trop Paediatr,* 17, 239-43, 1997

Zar, H., Langdon, G., Apolles, P., Eley, B., Hussey, G., Smith, P., Oral trimethoprim-sulphamethoxazole levels in stable HIV infected children, *SAMJ,* 96 (7), 627-9, 2006

☐ Team number ☐ House Number ☐ Village Number _____ Village Name

What do you think are this area's main problems?
What are the main health problems here?
What is the cause of these problems?

Where is the nearest clinic?	To whom do you go for help when you or your children are sick?
Can women go to the clinic?	
How long does it take to get there and how do you travel?	
When you get there, who is on duty?	What plants or other things do you use to treat sickness
Do they have medicines there?	Where can you get medicines?

For women

At what age do you start to give solid food your children?	Have you had a sister, a daughter or a mother who has died because of pregnancy or childbirth? If so, who died, what happened and when?
What foods do you give them? What age do you start which food?	
	Have you had any health problems which started due to childbirth?
When do you stop mother's milk completely?	Have you had any miscarriages?
Who helps to deliver babies in this community? Do they have any training?	Have you had any children who died in the first 4 weeks of life. If so, give date and name, and what happened

No	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
Name													
Relationship to head of house hold													
Age or year of birth													
Occupation													
Sex													
Have these people ever had any of the following diseases													
measles													
Whooping cough													
Cough for more than 3 months													
What vaccinations have they had which are recorded on a Vaccination Card													
DTP x 3													
PP x 3 drops													
BCG													
Measles													
TT													
Educational level													
At school now?													
Smoking													
Opium addiction													
Nasswar													
Goitre													
MUAC													

Deaths in last 7 years

Name	Date	Age	Cause

How much land do you have? Not Irrigated Irrigated	Where do you get your water for drinking?
What crops do you grow?	How far is it?
How many animals do you have? Donkeys Chickens Sheep Goats Cows	Has anyone gone to work away from here and send money back? Who and where?

Appendix 2: 2002 survey form completion guidance notes (composed for the focus groups - some questions were removed on the final form).

Guidance for Survey Completion

These are a few notes – not a complete guide.

Each surveyor will have survey forms, and a notebook. For each village, write the name and number of the village in the note book. Write down a description of the village - how many houses are there? Is it by the river, is it in the mountains, is it 'good land' for crops, or 'bad'? Is there a bazaar? Are there any shops at all, or a chai khana? Is water plentiful or scarce? What is the security situation?

We need to survey one third (33%) of the houses. When you arrive in the village, ask how many houses there are. If it is a small village, the whole team should go together and walk around with someone from the village, and with chalk, write a number on the door of each house. After the numbering has been finished, the team should write the numbers on small pieces of paper, fold them and put them into a bag. The total number of houses should be divided by 3, and if necessary round up. That is the number of pieces of paper you need to take out of the bag. For example, if there are 26 houses, you need to take 9 pieces of paper (26 divided by 3 is 8.66, rounded up to 9), if there are 13 houses, you need to take 4 pieces of paper. You must then complete the survey form for the houses whose number you took from the bag. It is very important that this process is done properly; you must only complete the form for the houses that are selected by taking pieces of paper. If you do anything else, the results of the survey will be less good. Many people will ask you to survey their house, even though it was not drawn from the bag. Please do not complete a form for any other houses other than those drawn from the bag on the pieces of paper.

For each house, **write in the notebook** the village name, the village number and the house number. Write the date and the time you visited. Write the name of the head of the household

1. Start on the side of the form which starts "Village Name". It is important to get an idea of the communities understanding of their problems before asking our own questions.

Page 1 of the form

2. Record the village name. Make sure you know the number of the village, and you have worked out with all those doing the survey how to number the houses.

3. Write brief but accurate notes of what people say about their understanding of the problems. Record some direct quotes from them, writing down the actual words that they say. If there is not enough room on the form, record it in the note book you have, but make sure you write down the village name and number and house number clearly in the note book. Record who is telling you this information. **Do not make suggestions.**

4. *"To whom do you go when your children are sick?"* Write down whether they take the child to a special person, or someone in the family. **Do not make suggestions** (for example, **do not** say "do you take a sick child to the Mullah?")

5. *"What plants or other things do you use to treat sickness?"* Write down the name they use, and any other name if you know it, and record which sicknesses they use it for. If possible, collect a sample of the plant and bring it with you, recording the local name clearly, and for which sicknesses it is used. If there is not enough room on the form, record it in the note book you have, but make sure you write down the village name and number and house number clearly in the note book.

6. *"Where can you get medicines?"* Write down the name of the place they can buy medicines, whether it is in a bazaar or shop, or just from a person, and write down how far away it is.

7. *"Where is the nearest clinic?"* Write down the name of the place and the name of the clinic. Do they have to pay to attend the clinic?

8. *Can women go to the clinic?* Write down "yes" if women are allowed to travel to the clinic, "no" if they cannot.

9. *"How long does it take to get there, and how do you travel?"* Write down how many hours or days by foot, donkey or jeep.

10. *"When you get there, who is on duty?"* Write down if there is a doctor, a nurse or any other person.

11. *"Do they have medicines there?"* Write down if there are medicines available, and how much they have to pay for them.

12. **The next section is for women only, and must be completed by the woman on the team. Please ask the questions and write down the answers in private, where there are no men present**. It may be best to do this right at the end of the meeting, after you have filled in the second page of the form.

13. *"Have you had a sister, a daughter or a mother who has died because of pregnancy or childbirth? If so, who were they, what happened and when?"* This is an important question to find out the problems of pregnancy and childbirth. If any of the women know someone who died in pregnancy, write down their name, when they died and what happened. Please write down all the names this woman used, and her husband's and father's names if possible. It may be that women do want to use the name of the woman who has died. If that is the case, please write down their father's name. If there is not enough room on the form, record it in the note book you have, but make sure you write down the village name and number and house number clearly in the note book. Write down who is telling you this information.

14. *"Have you had any health problems which started due to childbirth?"* Write down any health problems which the ladies thought were due to having children. If there is not enough room on the form, record it in the note book you have, but make sure you write down the village name and number and house number clearly in the note book.

15. *"Have you had any miscarriages?"* Write down the name of the woman and the number you give them in the table from the second page of the form, and the number of miscarriages, and if possible, the dates. Include in this number any children born dead.

16. *"Have you had any children who died in the first two weeks of life?"* Write down the number of children and how many days old they were when they died.

17. *"At what age do you start to give your children solid food?"* Write down the age of the children when solid food is started.

18. *"What foods do you give them?"* Write down the names of all the foods used for children in the first 3 months of taking solid food.

19. *"What age do you start which food?"* Write down the age that each food is started.

20. *When do you stop mother's milk completely?* Write down the age when mother's milk is stopped.

21. *"Who helps to deliver babies in this community? Do they have any training?"* Write down the name of any woman who goes from house to house to help with deliveries, if there is any. Write down any training these women have received, and when they received it. If only members of the household are involved, write that down.

Page 2 of the form

22. *"Name".* Write down the name that is used in the household, starting with the head of the household. **Also write down children who died before 5 years of age, and write "died" in the 'occupation' box**. If the person talking with you does not want to use the name of the child, just write 'child' and all the other details. If a man does not want to give his wife's name, write 'wife of ..." and his name. Put a circle around the number of the person who is telling you this information. If there are two or more people, put a circle round their numbers too. If there is one person who is giving you most of the information, put a cross over the number as well as a circle.

23. *"Relation to head of household".* Write down the relationship – for example, 'son', 'daughter', 'daughter in law', 'mother', 'grandson', 'cousin'.

24. *"Age or year of birth"* Write down the age in months, if there is a child under 2 years old, or in years. In the case of a child who has died, write down both year of birth, and the age at which they died.

25. *"Occupation".* Write down the occupation of each man over 14 years old, and of any women who have training, or who are in paid employment. If the person is under 14, write 'child'. If the person is a woman who works only in the home, write 'home'. If it is a child who died under the age of 5 years, write 'died'

26. *"Sex"* Write down "male" or "female"

27. ***The next 4 questions are about current and past illness.***

28. *"Measles"* If the person has had measles in the past, write 1, of the person has not, write 0.

29. *"Whooping cough".* If the person has had whooping cough in the past, write 1, of the person has not, write 0.

30. *"Cough for more than 3 months".* If the person has had a cough for more than 3 months, and is still coughing now, write 1, of the person has not, write 0.

31. ***The next 5 questions are about vaccinations***. Many people will have a vaccination card. You must check the names on the cards very carefully, to make sure you have the right person. If the person has had the vaccination, and it is recorded on the card, write 1. If the person has not had the vaccination, write 0.

32. "*Education level".* If the person completed 1st grade, write 1. If 2nd grade, write 2, 3rd grade, write 3 etc. If the person did not attend school, but can read and write, write L. If the person has no education, write 0.

33. *"At school now?"* If the person is attending school at the moment, write the class the person is in.

34. *"Smoking"* If the person smoke more than 5 cigarettes a week, write 1. If the person does not smoke cigarettes, write 0

35. *"Nasswar"* If a person uses nasswar, write 1. If a person does not use nasswar, write 0

36. *"Opium addiction"* If the person smokes or eats opium, or has smoked or eaten opium in the last 6 months, write 1. Write 1, even if they say that they are not addicted. If the person used to smoke or eat opium, but does not now, write X. If the person does not use opium, and has never done so, write 0.

37. *"Goitre"* If the person has a visible goitre, write 2. If the person has a goitre which is visble when the neck is stretched, and they swallow, write "1" If there is no goitre, write 0. (there is a separate guidance sheet on goiter)

38. *"MUAC"* (mid upper arm circumference) If the person is over 5 years old, write 0. If the child is under 1 year old, write 0. If the child is between 1 and 5 years old, measure the left arm using the tape. If the measurement is green, write G, if yellow, write Y, if red, write R (NB Final form asked for actual measurement)

39. *"Deaths in the last 7 years"* Write down the name of the person who died. If the person does not want to give the name of the person who died, write "old man", "old woman", "man", "woman", "boy", "girl", "male baby", "female baby". Write down the date they died, giving the year and the month if possible. Write down how old they were. Write down the cause of their death if possible.

40. If there are more than 13 people in the household, take another sheet, write the village name, village number and house number clearly on it and write down the details of other people on the second page of the sheet. Change the numbers of the people to 14, 15 16 and so on.

41. *"How much land do you have?"* Write down the number of jeribs of irrigated and not – irrigated land. Include land which is planted with crops, not land for grazing. Some people may want to give the answer as weight of seed. If that is so, try to find out how many seers of seed are sown per jerib of land in that village, and write the answer in the notebook.

42. *"What crops do you grow"* Write down the crops the household grows, and the number of jeribs planted with that crop last year.

43. *"How many animals do you have?"* Write down the number of chickens, goats, sheep and cows the household owns.

44. *"Where do you get your water for drinking"* Write down if the water comes from a well, a river, a canal, a spring or any other place. If it is a well or a spring, write down if it is protected or not.

45. *"How far is it?"* Write down the distance in minutes or hours.

46. *"Has anyone gone to work away from here and send money back? Who and where?"* Write down if anyone in the family gone away from this village to earn money to bring back or send back. If they have come back, or go every year, write down how long they spend there, and where they go.

47. If there is any other information which you think will be useful to understand the situation of the people in this area, village or house, write it down in your notebook, clearly giving the village name, village number and household number.

Appendix 3: text of the consent form

Consent form for sampling from children

Name of child Father's name

Age M/F

Father's name

Head of Household

Dr Alex wants to collect microbes to see if they are stronger than the antibiotics our health workers are using or weaker, so that we can ensure we use antibiotics which are sufficiently strong. Even when they are well, everybody has a very large number of microbes on their body and up their nose, and usually these do not cause problems; however, sometimes the microbes get into the wrong place and cause illness. The microbes will be taken by putting a very small piece of wire with a small piece of cotton on the end into your child's nose. It is not dangerous, and it does not hurt, although it is a bit uncomfortable, and the child may cry. Dr Alex will then examine the microbes in his laboratory, to see if the antibiotics are too weak or strong enough. Some of the microbes, or pieces of them, might be sent to England to another laboratory, where an expert will study them further but that place will not know which person they came from. In addition to this information, collecting these microbes may help Dr Alex to understand how microbes become stronger than antibiotics, and that may help lots of people in many places around the world to get the best medicines.

You are allowed not to agree to Dr Alex taking the microbes on the cotton; that is fine, and it will not affect the way Dr Alex gives medical treatment to your family. Even after the microbes have been taken, you can decide to ask Dr Alex not to carry on with his study on your child.

Please sign your name or put your thumb print at the bottom of this form. By doing so, you indicate that you are giving permission to Dr Alex to take the microbes from your child's nose, and for him to study them, and send them to England if necessary."

Signed or thumb,

Relationship to child date

Appendix 4: sample consent form in Dari (child's name blanked out)

فورم موافقت برای نمونه گیری از عضو خانواده ها

اسم
عمر – [redacted] سال
جنس – F
ولد – باقی
نیس خانواده عبدعلی

میکروب را که داکتر الکس تحت نام (اسم اطفال) جمع آوری کرده قوی تر ازیکی انتیبیتیک های میباشد که ما زیادتر در منطقه استفاده میکنیم. در این هنگام این خطرناک نمیباشد که میکروب ها وقت زیاد را در جای که میباشند سپری نمایند. داکتر الکس میخواهد که دریافت نماید که اگر دیگران هم در خانواده ها این نوع میکروب را داشته باشند و کوشش مینماید کشف نماید که این میکروب از اثر چی بوجود میاید برای انجام این کار داکتر الکس میخواهد که میکروب ها را از بینی تمام اطفال خانواده ها که از یک سال بزرگتر باشند جمع آوری نماید و این میکروب ها توسط یک سیم بسیار کوچک و یک پارچه نخی بسیار کوچک که در اخیر سیم میباشد به بینی داخل میشود و میکروب گرفته میشود.
این خترناک نبوده و کدام درد هم به طفلان وارد نمیکند با وجود این که معاینه نا راحت کننده میباشد و اطفال نوجوان شاید گریه هم بکنند. داکتر الکس همچنان میخواهد که کمی ادرار از هر شخص را بگیرد تا معاینه نماید که آیا میکروب ها در ادرار هم قوی میباشد. بعضی از میکروب ها و یا پارچه های ایشان شاید در انگلستان به لابراتوار فرستاده شود تا یک متخصص دیگر آنرا مورد مطالعه بیشتر قرار بدهد. مگر در آنجا فهمیده نمیشود که این میکروب از کدام شخص به وجود آمده است.

شما اجازه دارید که با نظریه داکتر الکس که میکروب ها را توسط پارچه نخی میگیرد موافق نباشید، این درست است.
اما این مطلب نمیباشد که داکتر الکس برای فامیل های شما معالجه توسط دوا انجام ندهد.
حتا اگر داکتر الکس میکروب ها را بگیرد شما تصمیم گرفته میتوانید که داکتر الکس را مانع این شوید که برای مطالعه خود بالای اطفال تان میکروب را با خود نبرد.

لطفاً امضا و یا شصت تان را در پائین این فورم بگذارید. که نشان دهی این میباشد که شما برای داکتر الکس اجازه میدهید که میکروب ها را از بینی شما و یا اطفال شما بگیرد برای مطالعه خود و یا در صورت که لازم باشد به انگلستان بفرستد.

محل امضا و یا شصت

روابط (در صورت که طفل باشد)

تاریخ 9-4-08